ผลของแคลเซียมและ/หรือไฮโดรคลอโรไธอะไซด์ต่อการควบคุมความดันเลือด 24 ชั่วโมง ในผู้ป่วยความดันเลือดสูงชนิดปฐมภูมิ

นางสาว สุธีวรรณ โหตกษาปน์กุล

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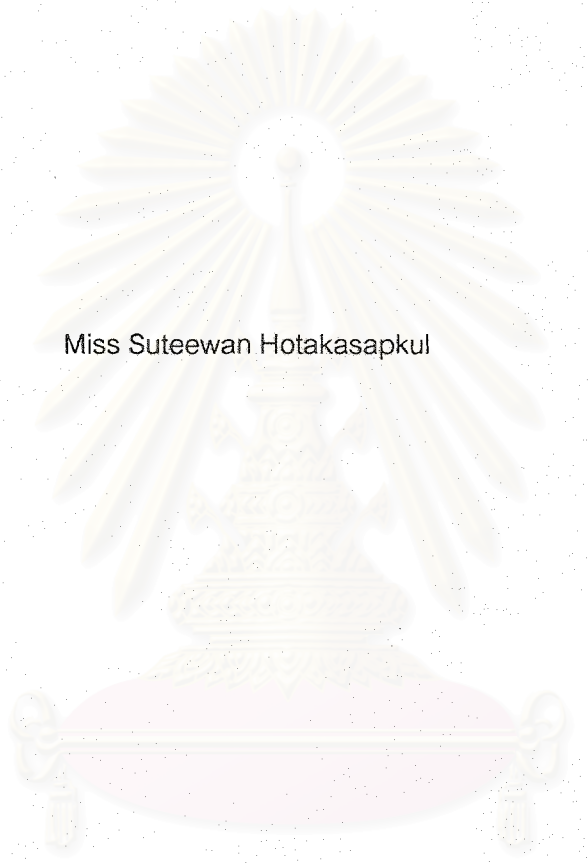
EFFECTS OF CALCIUM AND/OR HYDROCHLOROTHIAZIDE ON 24-HOUR BLOOD PRESSURE IN PATIENTS WITH PRIMARY HYPERTENSION

Miss Suteewan Hotakasapkul



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สุธีวรรณ โหตกษาปน์กุล : ผลของแคลเซียมและ/หรือไฮโดรคลอโรไธอะไซด์ต่อการควบคุมความดันเลือด 24 ชั่วโมงในผู้ป่วยความดันเลือดสูงชนิดปฐมภูมิ (EFFECTS OF CALCIUM AND/OR HYDROCHLOROTHIAZIDE ON 24-HOUR BLOOD PRESSURE IN PATIENTS WITH PRIMARY HYPERTENSION) อ. ที่ปรึกษา : รศ. ดร. ดวงจิต พนมวัน ณ อยุธยา, อ. ที่ปรึกษาร่วม : น.พ. สมเกียรติ แสงวัฒนาโรจน์ : 180 หน้า. ISBN 974-17-1073-9

การศึกษานี้มีวัตถุประสงค์เพื่อศึกษาผลเมื่อใช้เดี่ยวและเมื่อใช้ร่วมกันของแคลเซียมและไฮโดรคลอโรไธอะไซด์ต่อการควบคุมความดันเลือด 24 ชั่วโมง และความสัมพันธ์ระหว่างปริมาณโซเดียมและแคลเซียมที่ขับออกทางปัสสาวะกับผลการควบคุมเลือด 24 ชั่วโมง โดยใช้เครื่องมือวัดความดันเลือดอัตโนมัติชนิดพกพา ศึกษาในผู้ป่วยความดันเลือดสูงชนิดปฐมภูมิขั้นอ่อนและปานกลาง 25 ราย ณ แผนกผู้ป่วยนอก โรงพยาบาลจุฬาลงกรณ์ ใช้วิธีการสุ่มแบ่งผู้ป่วยเป็น 2 กลุ่ม คือ กลุ่ม1 จะได้รับยาไฮโดรคลอโรไธอะไซด์ 25 มิลลิกรัมต่อวันร่วมกับยาหลอก แคลเซียม กลุ่ม2 ได้รับแคลเซียม คาร์บอเนต 2 กรัมต่อวัน (คิดเป็น elemental calcium 800 มิลลิกรัมต่อวัน) ร่วมกับยาหลอกไฮโดรคลอโรไธอะไซด์ เป็นเวลา 4 สัปดาห์ จากนั้นผู้ป่วยกลุ่ม1 จะได้รับแคลเซียมแทนยาหลอก ส่วนกลุ่ม2 จะได้ยาไฮโดรคลอโรไธอะไซด์แทนยาหลอก เป็นเวลา 4 สัปดาห์เช่นกัน เมื่อรับประทานยาจนครบตามที่กำหนดแล้วจะทำการวัดความดันเลือดทั้งที่คลินิกและด้วยเครื่องวัดความดันเลือดอัตโนมัติชนิดพกพา ร่วมกับการเก็บปัสสาวะ 24 ชั่วโมงทุกครั้ง

ยาไฮโดรคลอโรไธอะไซด์ขนาด 25 มิลลิกรัมต่อวัน สามารถลดความดันเลือดได้ตลอด 24 ชั่วโมง ทั้งในผู้ป่วยที่ความดันเลือดสูงชนิดอ่อนและปานกลาง ลดความดันได้ดีในกลุ่ม non-dipper และเห็นผลชัดเจนมากขึ้นในกลุ่ม dipper โดยมีแนวโน้มลดความดันเลือด diastolic ได้ดีกว่า systolic ผลการลด BP loads สอดคล้องกับการลดความดันเลือด ส่วนเมื่อใช้แคลเซียมเสริมเดี่ยวๆ สามารถลดความดัน diastolic ดีกว่า systolic โดยเฉพาะในกลุ่มผู้ป่วยที่ความดันเลือดสูงชนิดอ่อนและกลุ่ม non-dipper ส่วนกลุ่ม dipper สามารถลดความดันเลือดได้ดีเฉพาะตอนกลางวัน ผลการลด BP loads สอดคล้องกับการลดความดันเลือด เมื่อใช้ร่วมกับไฮโดรคลอโรไธอะไซด์สามารถลดความดันเลือดและ BP loads ได้มากขึ้น โดยเฉพาะช่วงเวลากลางคืน ทั้งในกลุ่มผู้ป่วยความดันเลือดสูงชนิดอ่อนและกลุ่ม non-dipper แต่ไม่มีผลช่วยลดในผู้ป่วยความดันเลือดชนิดปานกลางและกลุ่ม dipper ส่วนการใช้ไฮโดรคลอโรไธอะไซด์ภายหลังจากที่ได้แคลเซียมเสริมก่อน พบว่าช่วยลดความดันเลือดและ BP loads ได้มากขึ้นแต่ผลการลดจะน้อยกว่าเมื่อใช้ไฮโดรคลอโรไธอะไซด์เป็นยาเดี่ยวๆ นอกจากนี้อัตราการตอบสนองและร้อยละของผู้ป่วยที่มีค่าความดันเลือดเข้าสู่เกณฑ์ปกติหลังจากได้รับยาทั้งสองชนิดร่วมกันมีค่าเพิ่มมากขึ้น

ยาไฮโดรคลอโรไธอะไซด์ขนาด 25 มิลลิกรัมต่อวัน เมื่อใช้เป็นยาเดี่ยวหรือเมื่อใช้เป็นยาตัวที่สองร่วมกับแคลเซียม สามารถเพิ่มการลดลงของความดันในช่วงกลางคืนได้ โดยเฉพาะในผู้ป่วยความดันเลือดสูงชนิดปานกลาง และกลุ่ม non-dipper ทำให้กลุ่ม non-dipper สามารถเปลี่ยนแปลงรูปแบบความดันเลือดไปเป็น dipper ได้เพิ่มขึ้นด้วย การใช้แคลเซียมเสริมเดี่ยวๆ จะช่วยเพิ่มการลดลงของความดันเลือดในช่วงกลางคืนได้ ในผู้ป่วยความดันเลือดสูงชนิดอ่อน และกลุ่ม non-dipper เท่านั้น ส่วนในกลุ่ม dipper จะส่งผลตรงข้ามกล่าวคือกลับทำให้การลดลงของความดันเลือดในช่วงกลางคืนน้อยกว่าช่วงก่อนได้รับยา ทำให้ผู้ป่วยบางคนเปลี่ยนแปลงรูปแบบความดันเลือดจาก dipper ไปเป็น non-dipper เมื่อมีการใช้ยาไฮโดรคลอโรไธอะไซด์ร่วมด้วยในภายหลัง สามารถลดความดันเลือดในช่วงกลางคืนได้เพิ่มขึ้นในผู้ป่วยทุกกลุ่ม ทำให้ผู้ป่วย non-dipper บางคนเปลี่ยนแปลงรูปแบบกลับมาเป็น dipper ดังเดิม

ยาไฮโดรคลอโรไธอะไซด์เมื่อใช้เป็นยาเดี่ยวหรือเมื่อใช้ร่วมกับแคลเซียม สามารถเพิ่มการขับปริมาณโซเดียมและลดการขับแคลเซียมออกทางปัสสาวะ โดยเฉพาะในกลุ่มผู้ป่วยความดันเลือดสูงชนิดปานกลาง ส่วนการให้แคลเซียมก่อนและให้ยาไฮโดรคลอโรไธอะไซด์ในภายหลังกลับทำให้การขับโซเดียมออกทางปัสสาวะมีปริมาณลดลงทั้งในกลุ่มผู้ป่วยความดันเลือดสูงชนิดอ่อนและชนิดปานกลาง ในกลุ่ม non-dipper การขับปริมาณโซเดียมจะเพิ่มขึ้น เมื่อมีการใช้ยาไฮโดรคลอโรไธอะไซด์หรือแคลเซียม เป็นยาเดี่ยวและเมื่อใช้ร่วมกัน ส่วนกลุ่ม dipper การขับปริมาณโซเดียมจะเพิ่มขึ้น เฉพาะเมื่อใช้ยาไฮโดรคลอโรไธอะไซด์เป็นยาเดี่ยวเท่านั้น

ภาควิชา.....เภสัชกรรม.....ลายมือชื่อนิสิต.....

สาขาวิชา.....เภสัชกรรมคลินิก.....ลายมือชื่ออาจารย์ที่ปรึกษา.....

ปีการศึกษา.....2545.....ลายมือชื่ออาจารย์ที่ปรึกษาร่วม.....

4376637833 : MAJOR CLINICAL PHARMACY

KEY WORD: HYDROCHLOROTHIAZIDE/CALCIUM SUPPLEMENT/HYPERTENSION

SUTEEWAN HOTAKASAPKUL: EFFECTS OF CALCIUM AND/OR HYDROCHLOROTHIAZIDE ON 24-HOUR BLOOD PRESSURE IN PATIENTS WITH PRIMARY HYPERTENSION. THESIS ADVISOR: ASSOC. PROF.DUANGCHIT PANOMVANA NA AYUDHYA, Ph.D. THESIS CO-ADVISOR: SOMKIAT SANGWATANAROJ, M.D. 180 PP. ISBN 974-17-1073-9

The purpose of this study was to examine the single and combined effects of calcium and hydrochlorothiazide (HCTZ) on 24-hour blood pressure and the relationship between 24-hour sodium and calcium urinary excretion and 24-hour blood pressure control using ambulatory blood pressure monitoring (ABPM) machine. The study was achieved in twenty-five mild to moderate hypertensive patients in out-patient department at King Chulalongkorn Memorial Hospital. They were randomly allocated into two regimens, twelve patients were assigned to receive HCTZ 25 mg once daily as the first drug while thirteen patients were assigned to receive $CaCO_3$ 1 gm twice daily (elemental calcium 800mg/d) as the first drug. Four weeks later, $CaCO_3$ 1 gm BID was added into the therapy for group 1, while HCTZ 25 mg OD was added into the therapy for group 2 for another 4 weeks. The office BP, 24-hour ambulatory BP and 24-hour urine collection were monitor at the end of each period.

HCTZ 25 mg OD could significantly reduce BP of the patients throughout 24-hour in both mild and moderate hypertensive patients, in non-dipper and especially in dipper group. DBP was slightly higher reduced than SBP. BP loads were similarly reduced in the same group of patients. $CaCO_3$ caused higher reduction in DBP than SBP especially in mild hypertensive and/or non-dipper patients while in dipper group it seem to cause more reduction during day-time than night-time. BP loads were reduced in the same way as blood pressure. When $CaCO_3$ was used as a second drug combined with HCTZ, there were increment in BP and BP loads reductions especially during night-time in mild hypertensive and/or non-dipper group while no further BP and BP loads reductions were found in moderate hypertensive and/or dipper group. When HCTZ was used in combination with $CaCO_3$, the increment of BP and BP loads reduction was much less than when HCTZ was used as the first drug. Greater rate of response and higher percentage of normalized patients were found after treatment with the combination drugs.

HCTZ 25 mg per day alone or used in combination with $CaCO_3$, the nocturnal decline of BP were increased in moderate hypertensive and/or non-dipper patients, the circadian rhythm of blood pressure of non-dippers might be transformed to dipper patterns. $CaCO_3$ alone could increased nocturnal decline of BP only in mild hypertensive and/or non-dipper group. In contrary, in dipper group, the nocturnal decline of BP not only not increased but even became lower than baseline, the BP pattern of some dippers was therefore was change to non-dipper. After HCTZ was added to the therapy with $CaCO_3$, the increment of nocturnal decline of BP were increased in all groups of patients, the BP pattern was thus changed back to dipper type.

24-hour urinary sodium excretions were increased after treatment with HCTZ either alone or combined to $CaCO_3$, especially in moderate hypertensive patients. In contrary, when $CaCO_3$ was used as the first drug and HCTZ was added to the therapy, the 24-hour urinary sodium excretion were decreased in both mild and moderate hypertensive patients. 24-hour urinary sodium excretion of non-dippers were lower while the excretion of calcium were higher as compared to dippers. Sodium excretion in non-dipper were increased after treatment with HCTZ or $CaCO_3$ alone and when used the two drugs in combination, however, in dippers, the increment in sodium excretion was found only after treatment with HCTZ alone.

Deparment.....Pharmacy.....Student's signature.....Suteewan Hotakasapkul

Field of study.....Clinical pharmacy.....Advisor's signature.....Duangchit Panomvana

Academic year.....2002.....Co-advisor's signature.....Somkiat Sangwatanaroj

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Suteewan Hotakasapkul

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LIST OF ABBREVIATION

ABP	ambulatory blood pressure
ABPM	ambulatory blood pressure monitoring
ALT	alanine aminotransferase
AST	aspartate aminotransferase
bpm	beat per minute
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
Cr	creatinine
DBP	diastolic blood pressure
hr	hour
HCTZ	Hydrochlorothiazide
HDL	high density lipoprotein
HR	heart rate
Ht	height
mg	milligram
mmHg	millimeter mercury
min	minute
MAP	mean arterial pressure
MDBP	mean diastolic blood pressure
MSBP	mean systolic blood pressure
no	number
OBP	office blood pressure
RDA	recommended dietary allowance
SBP	systolic blood pressure
SD	standard deviation
Wt	weight

CHAPTER I

INTRODUCTION

Hypertension is the most frequently encountered chronic medical condition and is also one of the most significant risk factors for cardiovascular morbidity and mortality from coronary artery disease (ischemic heart disease, myocardial infarction [MI], sudden death), cardiac disease (left ventricular hypertrophy [LVH], congestive heart failure [CHF]), renal failure, stroke, and blindness. Considerable effort has been directed at determining the incidence, prevalence, and hazards of hypertension and identifying determinants and optimal treatments for hypertension remain an important concern of national healthcare.[1] High blood pressure was responsible for over 42,565 Americans death in 1997 and may have contributed to another 210,000 deaths.[2] The death rate from high blood pressure is estimated to have increased by 13.1% between 1987 and 2000.[3] Data from the National Health and Nutrition Examination survey (NHANES)III document a low rate of blood pressure goal achievement: 27.4% of those on treatment for hypertension achieved a goal of < 140/90 mm Hg.[4] Among patients with diabetes, INVEST trial indicated that the target systolic blood pressure goal of less than 130 mm Hg was met by 34% and the diastolic goal of less than 85 mm Hg was met by 83% of patients.[5] Recent data from the Hypertension Optimal Treatment (HOT) trial demonstrate that the lowest cardiovascular even rate occurred when diastolic blood pressure was reduced to 83 mm Hg or lower. In patients with diabetes mellitus, cardiovascular events were reduced 51% in patients assigned a goal diastolic blood pressure of ≤ 80 mm Hg compare with patients who achieved a diastolic blood pressure of ≤ 90 mm Hg (p=0.005).[6] So that, the new treatment recommendations published by The National

Kidney Foundation (NKF) Hypertension and Diabetes Executive Committee Working Group, physician are urged to take a more aggressive approach to treating patients with both high blood pressure and diabetes achieved the recommended goal blood pressure level from 130/85 mm Hg to 130/80 mm Hg.[7,8] A problem in the management of hypertension is the failure to achieve better blood pressure control rates.[4,7] There are many reasons for the failure such as cultural, educational, ethnic, and religious factors on the part of the patients and fear of side effects, lack of understanding of the benefits of lowering blood pressure, and lack of diligence on the part of many physicians.[7,9]

JNC-VI, released in November 1997 by The National High Blood Pressure Education Program(NHBPEP)[10] and The World Health Organization and the International Society of hypertension (WHO-ISH)[11] suggested that treatment to lower blood pressure levels may be useful, particularly to prevent stroke, to preserve renal function, to prevent or slow heart failure progression, and reduce target organ damage(TOD). The EISBERG (Evaluation and Interventions for Systolic Blood Pressure Elevation-Regional and Global) project indicated that an average reduction of 12 to 13 mm Hg in systolic blood pressure over 4 years of follow-up is associated with a 21% reduction in coronary heart disease, 37% reduction in stroke, 25% reduction in total cardiovascular death, and 13% reduction in all-cause deaths.[12] Ambulatory blood pressure monitoring (ABPM) involves the use of a non-invasive device which is use to measure continuously monitor changes in blood pressure during the routine activities of daily living.[13] A patient's 24-hour ambulatory blood pressure profile correlates better with end-organ damage such as ventricular hypertrophy and proteinuria than do casual office measurement.[10,13-19]

Blood pressure in normotensive individuals who follow a typical sleep-wake cycle (awake during the day and asleep at night) exhibits a characteristic circadian pattern, exemplified by a sharp increase during the early morning hours (upon awakening) that reaches a plateau around 1100 h. After this, the blood pressure level gradually declines, reaching its lowest value around 2400 h.[13,15,,20-23] In patients with essential hypertension, it has been postulated that the absent or diminished blood pressure fall during night-time (non-dipper) is associated with increased end-organ damage, such as left ventricular hypertrophy, microalbuminuria, and cerebrovascular diseases than occurs in patients whose blood pressure decrease 10% or more during the night (dipper).[13,15,17,23]

Recently, study also showed that in patients with sodium-sensitive essential hypertension, blood pressure fails to fall during the night may be marker of greater risk of renal and cardiovascular complications, as has been found in non-dippers.[24-27] Although the mechanism of salt-sensitive hypertension has not been fully clarified, proposed mechanisms include expansion of fluid volume[28], impairment of the L-arginine-nitric oxide is associated with endothelial dysfunction[29-32],alteration in the renin-angiotensin aldosterone system, alterations function of the sympathetic nervous system[28,33],involvement of endothelin systems[34-36], and insulin resistance may result from inherited abnormalities of intracellular calcium metabolism.[28,33,37-38] The NaCl loading blunted the nocturnal decline in blood pressure.[39] Sodium reduction could offer a valuable non-pharmacological approach to lowering blood pressure.[10,40-48] The diminish nocturnal fall, recognized in the salt-sensitive type, is restored by sodium restriction, indicating that the circadian rhythm of blood pressure shifted from a non-dipper to a dipper pattern.[49]

Diuretic-based treatment of patients with hypertension prevents the development of cardiovascular complication and has been recommended as first-choice medications in the management of hypertension.[10] It has been demonstrated that diuretics can restore nocturnal blood pressure decline in manner similar to sodium restriction, and data from Japanese study suggested that diuretic therapy with hydrochlorothiazide indicating that the circadian rhythm of blood pressure shifted from non-dipper to dipper patterns.[50] Recently, data concluded that five broad categories consistently associated with salt sensitivity. These include 1. Demographic factors (increase age, increase weight, female) 2. Racial factors (markedly in African American than Caucasians) 3. Renal function factors 4. Hormonal factors (increase norepinephrine, decrease dopamine, decrease kallikrein) and 5. Dietary habit factor (decrease calcium and potassium intake).[51] In almost epidemiologic studies, low dietary calcium intake is associated with an increased prevalence of hypertension.[52] The National Heart, Lung, and Blood Institute (NHLBI) conducted DASH diet, which emphasizes fruits, vegetables, and low-fat dairy foods; includes whole grains, poultry, fish, and nuts; reduced in red meat, sweets, and sugar-containing beverages. It is rich in magnesium, potassium, and calcium as well as protein and fiber.[44] After that, data indicated that calcium supplement of 800-1200 mg/d significantly decrease of systolic blood pressure both for hypertensive persons and for overall sample[53-55] and the other studies shown that calcium supplement prevents salt-induced high blood pressure and platelet hyperaggregability, with a suppression of the platelet reaction. The beneficial effects of oral calcium for reducing thrombotic cardiovascular risk[56] and ischemic stroke.[57]

The previous works mentioned above had shown the importance of monitoring blood pressure response by 24-hour ambulatory measurement and the effect of hydrochlorothiazide and calcium intake on circadian blood pressure. However, data on the single and combined effects of calcium and hydrochlorothiazide on circadian blood pressure rhythm in Thai patients with primary hypertension doesn't have.

Objectives

1. To examine the effects of hydrochlorothiazide on 24-hour blood pressure in primary hypertension patients
2. To determine the effects of calcium supplement on 24-hour blood pressure in primary hypertension patients
3. To investigate the effects of hydrochlorothiazide combine calcium supplement on 24-hour blood pressure in primary hypertension patients
4. To describe the relationship between 24-urinary excretion of sodium and calcium on 24-hour blood pressure

CHAPTER II

REVIEW OF LITERATURE

1. Hypertension

Hypertension is the most frequently encountered chronic medical.[1] Its occurrences in the United States increases with age, and it is more prevalent in African Americans compared to Caucasians[51] and in the lesser educated[2,9,12,41] and lower socioeconomic status.[2,12,41]

Blood pressure is a continuous variable, it is impossible to define a cut point below which the blood pressure is normal and above which the pressure is abnormally high. The diagnosis of hypertension is confirmed when the average of two or more diastolic blood pressure (DBP) measurements visits are 90 mm Hg or higher and/or the average of two or more systolic blood pressure (SBP) measurements are 140 mm Hg or greater than.[1,14]

Blood pressure varies with environment temperature, the time of day, the timing of meals, physical activity, posture and emotions. An individual who exhibits a defense reflex in a medical setting may experience a rise in blood pressure that returns to normal outside the medical setting. This is known as "white coat" hypertension. White coat hypertension appears to occur in approximately 20% of newly diagnosed hypertensive patients. White coat hypertension is more likely to occur in young, female patients who do not have a long history of hypertension.[1,10,14] Suspected white coat hypertension is one of a limited number of indications for which ambulatory blood pressure monitoring may be warranted. A patients 24-hour blood pressure profile correlates better with end-organ damage than do casual office measurement, current limitations prohibit routine use of such technology.[13-22]

1.1 Prevalence of hypertension

The prevalence of hypertension depends on both the racial composition of the population studied and the criteria used to define the condition.[58] As many as 50 million Americans have high blood pressure (>140/90 mm Hg). Blood pressure increase with age, but the onset of hypertension most often occurs during the third, fourth, and fifth decades of life. An even higher prevalence has been documented in the blacks population than whites.[14] In female the prevalence is closely related to age, with a substantial increase occurring after age 50.[58] In the elderly population (age > 65 years), gender differences in blood pressure are less marked.[14] Data from the 1976 to 1980 and 1988 to 1991 of The National Health and Nutrition Examination Survey (NHANES III)[4] indicated that the prevalence of hypertension decreased from approximately 58 million to around 50 million. The NHANES III reported that 35% of those with hypertension were unaware and only 53% of those with hypertension were receiving antihypertensive therapy, and in only 24% of those with hypertension had their blood pressure controlled to less than 140/90 mm Hg.

1.2 Etiology of hypertension[1,14]

Most persons with hypertension have no identifiable cause of disorder (termed primary or essential hypertension). However, various neural and humoral factors are known to influence blood pressure in Table 1. Patients have secondary hypertension when a specific cause for elevated BP has been identified in Table 2. Although only 5 to 10% of the hypertensive population have a secondary cause, patients should be further

evaluated if physical or laboratory findings are consistent with a secondary cause in Table 3. Further diagnosis workup also should be considered in patients who do not respond to increasing doses of antihypertensive medication, or who have a sudden increase in BP or accelerated or malignant hypertension. A thorough review of the patient's prescription and nonprescription medications should be conducted to rule out drug-induced BP elevations (see Table 2).

The pathogenesis of essential hypertension remains mysterious, a specific cause of sustained hypertension cannot be found. It is likely that several interrelated mechanisms rather than a single causative defect, control blood pressure in essential hypertension. In fact that hypertension often runs in families suggests that genetic factors may play an important pathogenic role in the development of essential hypertension. There is even some evidence that single genes might be responsible for specific subtypes of hypertension. These include genetic traits for high sodium-lithium counter transport, a low urinary kallikrein excretion, increased aldosterone and other adrenal steroid, and high angiotensin levels. Identifying individuals with these traits could lead to more direct approaches for preventing or treating hypertension.

Table 1: Mechanisms involved in arterial blood pressure

Hemodynamic	CO, PVR
Adrenergic nervous system	CNS, α-receptors, peripheral α- and β-receptors
Renin-angiotensin-aldosterone system	Regulates systemic and renal blood flow via Angiotensin II-mediated vasoconstriction; aldosterone stimulates sodium and fluid retention
Renal function and renal blood flow	Fluid and electrolyte balance
Hormonal factors	Adrenal cortical hormones, vasopressin, thyroid, insulin
Vascular endothelium	Nitric oxide, bradykinin, prostacyclin, endothelin

CNS, central nervous system; CO, cardiac output; PVR, peripheral vascular resistance.

Reprinted from reference 1.

Table 2: Secondary cause of hypertension

Renal disease	*Drug-induced*
Renoparenchymal disease	Adrenalcorticosteroids
Renovascular disease	Alcohol
Coarctation of the aorta	Amphetamines/anorexiants (e.g. phentermine, sibutramine)
Primary aldosteronism	Appetite suppressants (including some herbal products containing ephedra, caffeine, and MaHuang)
Cushing's syndrome (Hyperadrenalism)	Cyclosporine, Estrogens ,Licorice
Pheochromocytoma (Adrenal tumor)	MAOIs, NSAIDs, Oral contraceptives
Pregnancy	Oral decongestants (e.g. pseudoephedine, Phenylpropranolamine)
Increased intracranial pressure	Thyroid hormone excess, TCAs
	Venlafaxine

MAOIs, monoamine oxidase inhibitors; NSAIDs, non-steroidal anti-inflammatory drugs; TCAs, tricyclic antidepressants.

Reprinted from reference 1.

Table 3: Clinical findings suggestive of secondary hypertension

Correctable causes	Historical finding	Physical examination finding	Laboratory finding
Estrogen use	Oral contraceptive use or postmenopausal hormone replacement therapy		
Renovascular disease	Moderate or severe HBP before age 30 or after age 55; rapidly progressive HBP	Abdominal bruits[a] with ↑ systolic and diastolic pressure; fundoscopic hemorrhages	Suppressed or stimulated Plasma renin activity; IVP (rapid sequence); digital subtraction angiography
Renoparenchymal disease	Dysuria, polyuria, nocturia; Urinary tract infection; renal stones(or colic); family history-polycystic kidney disease; renal disease	Edema	Proteinuria; hemaruria; bacteriuria
Coarctation of the aorta	Intermittent claudication	Diminished or absent femoral pulses compared with carotids. Lower systolic leg BP compared with arm BP	
Pheochromocytoma	Paroxysmal headaches, Palpitation, sweating, dizziness, and pallor (in 30% of patients)	Nervousness, tremor, tachycardia, orthostatic hypotension	Clonidine suppresstion test[b]; ↑serum glucose, high urine metanephrine or vanillylmandelic acid
Primary aldosteronism	Weakness, polyuria, polydipsia, intermittent paralysis	Orthostatic hypotension	Hypokalemia
Cushing's syndrome	Menstrual irregularity	Moon face; truncal obesity; Buffalo hump; hirsutism; violet striae	↑ serum glucose; ↑ plasma cortisol after suppression with dexamethasone

[a] Most abdominal bruits do not originate from the renal artery.

[b] Failure of plasma catecholamines to ↓ by 50% within 3 hour of administration of 0.3 mg clonidine highly pheochromocytoma

BP, blood pressure; HBP, high blood pressure; IVP, intravenous pyelogram.

1.3 Pathophysiology[14]

Multiple factors may contribute to the development of primary hypertension including abnormal neural mechanisms; defects in peripheral autoregulation; malfunctions in either humoral or vasodepressor mechanisms; and disturbance in sodium, calcium, and natriuretic hormone.

1.3.1 The neural components[1,14]

Both the central (CNS) and the autonomic nervous systems are intricately involved in the maintenance of arterial blood pressure. Stimulation of certain areas within the CNS (nucleus tractus solitarius, vagal nuclei, vasomotor center, and the area postrema) can result in either an increase or a decrease in blood pressure. For example, α_2-adrenergic stimulation within the CNS decreases blood pressure through an inhibitory effect on the vasomotor center. Increased angiotensin II, however, increases sympathetic outflow from the vasomotor center, which eventuates in an increase in blood pressure. Located on the presynaptic surface of sympathetic terminals are a variety of receptors that either enhance or inhibit norepinephrine release. The α and β presynaptic receptors play a role in negative and positive feedback to the norepinephrine-containing vesicles located near the neuronal ending. Stimulation of presynaptic α- (α_2)-receptors exerts a negative inhibition on norepinephrine release. Stimulation of presynaptic β-receptors facilitates further release of norepinephrine. The α- and β- receptors are also located on the surface of effector cells innervated by sympathetic neuronal fibers. Stimulation of postsynaptic α- (α_1)-receptors on arterioles and venules results in

vasoconstriction. These are two types of postsynaptic β- receptors, β_1 and β_2. Both types of β- adrenergic receptors are presented in all tissue innervated by the sympathetic nervous system; however the distribution of β_1- and β_2- receptors is such that in some tissue β_1- receptors predominate and in other tissue β_2- receptors predominate. Stimulation of β_1- receptors in the heart results in an increase in heart rate and contractility. When β_2- receptors in the arterioles and venules are stimulated, vasodilation occurs.

The major negative-feedback mechanism controlling sympathetic activity is the system of baroreceptor reflexes. Baroreceptors are nerve endings lying in the walls of large arteries, especially in the carotid arteries and aortic arch. The baroreceptors respond extremely rapidly to change in arterial pressure. Baroreceptor impulses are transmitted to the brainstem primarily through the ninth cranial nerve and vagus nerve. In this reflex system, an acute elevation in arterial pressure increases the rate of baroreceptor discharge, which results in vasodilation throughout the peripheral circulatory system and a decrease in heart rate and myocardial contractility. Conversely, low pressure has the opposite effect, causing reflex vasocontriction and an increase in heart rate and force of contraction. These baroreceptor reflex mechanisms may be blunted in elderly individuals. A pathologic disturbance in any of these neural components that modulate arterial blood pressure. It is reasonable to postulate that the primary defect can occur in any of the four major components: CNS, autonomic nerve fibers, adrenergic receptors, or baroreceptors. Also, because they are so physiologically interrelated, a defect in one component may

disturb the normal function in an other, and the combined abnormalities may then cause hypertension.

1.3.2 The peripheral autoregulatory components[1,14]

Abnormalities in either the renal or tissue autoregulatory processes could cause hypertension. In fact, it seems reasonable to postulate that individuals may first develop a renal defect for sodium excretion and then reset their tissue autoregulatory processes to a higher arterial blood pressure. Normally, the volume-pressure adaptive mechanism of the kidney works well to maintain a normal blood pressure. When the blood pressure drops, the kidneys adapt by retaining more sodium and water. This leads to plasma volume expansion, which increase blood pressure. Conversely, when blood pressure rises above normal, sodium and water excretion are increases, plasma volume, and cardiac output are reduced, and the blood pressure returns to normal. An initial defect in the renal adaptive mechanism could lead to plasma volume expansion and increase blood flow to peripheral tissue even when blood pressure is normal. To offset the increase in blood flow, local tissue autoregulatory processes would induce arteriolar constriction to raise the peripheral vascular resistance. In time, a thickening of the arteriolar walls may occur, resulting in a sustained elevation in peripheral vascular resistance. An increase in total peripheral vascular resistance is a common underlying problem in patients with primary hypertension.

1.3.3 The humoral mechanisms

At least three possible humoral abnormalities may be responsible for causing primary hypertension in some individuals.

1.3.3.1 The renin-angiotensin-aldosterone system (RAS)[14,58]

The RAS is important to the regulation of sodium, potassium, and fluid balance, and it significantly influences vascular tone and sympathetic nervous system activity. In the kidney, renin is synthesized and stored in the juxtaglomerular cells, which are located primarily in the media of the renal afferent arterioles. Several factors are known to control renin release. These can be grouped into intrarenal factors (such as perfusion pressure, catecholamines, angiotensin II) and extrarenal factors (such as sodium, chloride, and potassium).

Angiotensin II has been shown to directly inhibit the release of renin through negative feedback. Catecholamines increase renin release probably by directly stimulating the juxtaglomerular cells through an action involving the formation of cyclic AMP. Both potassium and calcium may also play a direct role in renin release. Decreased serum potassium or intracellular calcium stimulates renin release by the juxtaglomerular cells.

In blood, renin catalyzes the conversion of angiotensinogen to angiotension I, which is then converted to angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II exerts its biologic effects in various tissues following binding to specific receptors classified as AT_1 or AT_2 subtypes.

The AT_1 receptor is located in brain, renal, myocardial, vascular, and adrenal tissue. The AT_2 receptor is located in adrenal medullary tissue, uterus, and brain. AT_1 receptors mediate the majority responses critical to cardiovascular and renal function. An increase in circulating angiotensin II can cause an elevation in blood pressure through both pressor and volume effects. The pressor effects of angiotensin II include direct vasoconstriction, stimulation of catecholamine release from the adrenal medulla, and a centrally mediated increase in sympathetic nervous system activity. Angiotensin II also stimulates the release of aldosterone from the adrenal gland, which leads to retention of both sodium and fluid, with a resultant increase in plasma volume and blood pressure. Clearly, any disturbance in the RAS that leads to an increase in any or all three components could produce hypertension (see figure 1).

Both the heart and brain contain a local RAS. In the heart, angiotensin II is also generated by a second enzyme, angiotensin I convertase (human chymase), which is not blocked by ACE inhibition. Activation of the myocardial RAS leads to increased cardiac contractility and stimulation of cardiac hypertrophy. The brain RAS has at least two functions. Angiotensin II modulates the production and release of hypothalamic and pituitary hormone. Angiotensin II also enhances sympathetic outflow from the medulla oblongata.

Local generation of biologically active angiotensin peptides in peripheral tissues may play an important role in the increased vascular resistance often observed in hypertensive individuals. There is also some evidence that

angiotensin produced by local tissue may interact with other humoral regulators and endothelium-derived growth factors to stimulate vascular smooth muscle growth and metabolism. This is situ generation of angiotensin peptides may, in fact, underlie the development of increased vascular resistance in froms of hypertension that are associated with low plasma renin activity. Components of tissue RAS may be responsible for long-term adaptation to hypertension (i.e., left ventricular hypertrophy, smooth muscle hypertrophy of blood vessels, and glomerular hypertrophy)

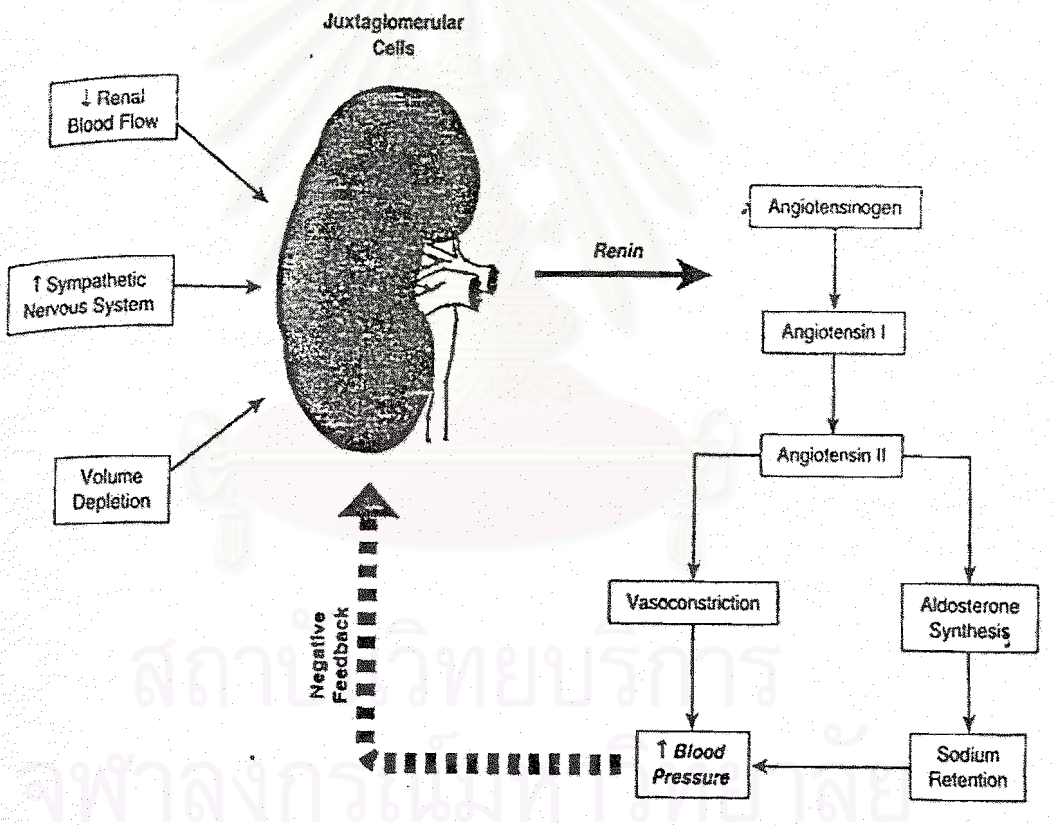

Figure 1: Overview of the renin-angiotensin-aldosterone system and blood pressure regulation[1]

1.3.3.2 Natriuretic hormone [1,14]

Another humoral factor that may be involved in the development of primary hypertension is the increased concentration of natriurtic hormone. The proposed role of natriuretic hormone is to inhibit Na^+/K^+-ATPase and, thus, to interfere with sodium transport across cell membranes. It has been suggested an inherited defect in the kidney's ability eliminate sodium would cause an increase extracellular fluid and plasma volume, as discussed earlier. This may cause compensatory increase in the concentration of circulating natriuretic hormone, which would increase urinary excretion of sodium and water. This same hormone, however, is also through to block the active transport of sodium out of arteriolar smooth muscle cells. The increased intracellular concentration of sodium and calcium would ultimately lead to increased vascular tone and hypertension.

1.3.3.3 Insulin resistance and hyperinsulinemia [1,14,58]

Evidence linking insulin resistance and hyperinsulinemia to the development of hypertension is mounting. Several possibilities by which hyperinsulinemia may lead to hypertension include renal sodium retention, enhanced sympathetic nervous system activity, and induction of vascular smooth muscle hypertrophy. Another possible way by which insulin could raise blood pressure is by increasing intracellular calcium concentration, which leads to increased vascular resistance. Hyperinsulinemia often accompanies upper body obesity, but even non-obese hypertensive individuals have been shown to be insulin resistant, glucose intolerant, and

hyperinsulinemic. The mechanism by which insulin resistance and hyperinsulinemia occur in hypertension is unknown. Hyperinsulinemia is also associated with hypertriglyceridemia, which results in a decreased concentration of HDL cholesterol.

1.3.4 The vascular endothelial mechanisms

The abnormalities in the structure and function of the vasculature are increasing recognized as contributing to the hypertensive state by increasing total peripheral resistance. During the past decade, it has become obvious that the endothelium, the single cell, innermost layer of blood vessels, is more than a passive barrier between the blood and the vascular smooth muscle. We now know that the endothelium plays a crucial role in circulatory homeostasis responding not only to humoral and chemical signals, but also to changes in the haemodynamics of blood flow such shear stress. Endothelial cells release chemical mediators that modulate the responses of numerous cells including vascular smooth muscle, platelets, and leucocytes. The endothelium serves a dual role in the control of vascular tone, endothelium cells produce and release a variety of vasoactive substances. These include vasodilators, such as endothelium-derived relaxing factor (EDRF) which has now been identified as nitric oxide (NO), endothelium-derived hyperpolarizing factor (EDHF), and prostacyclin, and vasoconstrictors, such as thromboxane A_2 and prostaglandin H_2, endothelin, and angiotensin II. The interaction between these vasodilators and vasoconstrictors provides a local control mechanism that regulates vascular tone. Alteration in the production of these mediators are involved in the induction and persistance of hypertension in both

experimental models and humans, in addition this endothelial cell dysfunction has been reported in various forms. Plasma levels of endothelin, for example, have been reported to be significantly higher in patients with primary hypertension. In addition, both chemical-stimulated and basal release of EDRF has been shown to be severely attenuated in hypertensive patients as well as in experimental models of hypertension. Another abnormality in the biology of vascular smooth muscle cells that may account for increased vasotone of hypertensives, is a disturbance in the physio-chemical properties of the cell membrane leading to abnormalities in ion handling. Reported abnormalities of cellular electrolyte homeostasis, for example, increased sodium influx due to elevation of sodium-hydrogen exchange activity, decreased sodium-potassium cotransport, increased lithium-sodium countertransport and decreased red cell membrane binding of calcium.

The parallel with studies on the function of vascular smooth muscle in the hypertensive state, considerable attention has been given to the importance of structural changes. The change in the geometry of the vessel wall that results in an increased vasoconstrictor response with the same degree of shortening of vascular smooth muscle in hypertensive patients is a decrease in the lumen (internal radius of the vessel). In studies of small resistance vessels from subcutaneous tissue from hypertensive subjects, an average 29% increase in the media thickness: lumen diameter ratio was found, closely matching the 32% elevation in blood pressure. The increase in the media thickness: lumen diameter ratio can result from an increase in wall thickness either due to medial smooth muscle cell proliferation, accumulation of glycoaminoglycan, or from the

increasing evident support to the role of rearrangement of a normal amount of tissue around a small lumen, a process known as remodelling.

1.3.5 Influence of dietary sodium, calcium, and potassium on BP[10,14,19,58-59]

The evidence linking excess sodium to the development of hypertension is based on both epidemiologic studies and clinical experiments. In general, population studies indicate that high salt intake is associated with a high prevalence stroke and hypertension and low salt intake is associated with a low prevalence of hypertension. Clinical studies have consistently shown that restriction of salt intake in the diet lowers blood pressure in many (but not all) subjects with hypertension. The exact mechanism by which excess sodium leads to the natriuretic hormone hypothesis discussed before. It has been proposed that an increased sodium intake together with an inherited defect in the kidney's ability to excrete sodium leads to a substantial increase in circulating natriurtic hormone. As previously mentioned, natriuretic hormone inhibits intracellular sodium transport, which causes increased vascular reactivity and, consequently, a rise in blood pressure.

Altered calcium homeostasis may also play an important role in the pathogenesis of hypertension. The calcium hypothesis states that a lack of calcium in the diet leads to a disturbance in the balance between intracellular and extracellular calcium. This imbalance is characterized by an increased intracellular concentration of calcium, which leads to altered vascular smooth muscle function and increased peripheral vascular resistance. Some studies have shown that supplementing the diet with calcium

results in a modest decrease in the blood pressure of hypertensive subjects. More research is needed to clarify the role of altered calcium homeostasis in causing hypertension in humans.

The role of potassium fluctuations is also inadequately understood. Potassium depletion may cause an increase in peripheral vascular resistance, but the clinical impact of small changes in the serum potassium concentration in not clearly defined. Furthermore, very limited data have suggested that potassium supplementation is associated with a reduced incidence of stroke, but this issue needs further study before supplementation can be endorsed.

1.4 Clinical presentation[14]

Patients with uncomplicated, primary hypertension are usually asymptomatic initially. While a complete history and physical examination may help identify concerns that warrant further evaluation, a few basic tests should be performed in all hypertensive patients prior to initiating drug therapy. These include hemoglobin and hematocrit, urinalysis, serum potassium and creatinine, liver function tests, and electrocardiogram. Total and high-density-lipoprotein cholesterol, plasma glucose, and serum uric acid are indicated to assess other risk factors and to develop baseline data for monitoring drug-induced metabolic changes. As the hypertension progresses, however, symptoms characteristic of cardiovascular, cerebrovascular, or renal disease may occur as the patient develops target organ damage. Patients with secondary hypertension usually complain of symptoms suggestive of the underlying disorder. For example, many

patients with pheochromocytoma have a history of paroxysmal headaches, sweating, tachycardia, and palpitations occurring singly or in combinations. More than half of the patients with this form of secondary hypertension suffer episodes of orthostatic dizziness or syncope. In primary aldosteronism, hypokalemic symptoms usually include muscle cramps and muscle weakness. Patients who present with hypertension secondary to Cushing' syndrome may complain of weight gain, polyuria, edema, menstrual irregularities, recurrent acne, or muscle weakness. The most common causes of secondary hypertension are summarized in Table 2.

Frequently, the only sign of primary hypertension is an elevated blood pressure. The rest of the physical examination may be completely normal. Again, as the hypertension progresses, signs of end-organ damage begin to appear. These are chiefly related to pathologic changes in the eye, brain, heart, kidneys, and peripheral blood vessels.

1.5 Effects of hypertension[58]

Patients with hypertension die prematurely; The most common cause of death is heart disease, with stroke and renal failure also frequent, particularly in patients with significant retinopathy.

1.5.1 Effects on the heart

Cardiac compensation for the excessive workload imposed by increased systemic pressure is at first sustained by concentric left ventricular hypertrophy, characterized by an increase in wall thickness. Ultimately, the function of

this chamber deteriorates, the cavity dilates, and the symptoms and signs of heart failure appear. Angina pectoris may also occur because of the combination of accelerated coronary arterial disease and increased myocardial oxygen requirements as a consequence of the increased myocardial mass. On physical examination, the heart is enlarged and has a prominent left ventricular impulse. The sound of aortic closure is accentuated, and there may be a faint murmur of aortic regurgitation. Presystolic (atrial, fourth) heart sounds appear frequently in hypertensive heart disease, and a protodiastolic (ventricular, third) heart sound or summation gallop rhythm may be present. Electrocardiographic changes of left ventricular hypertrophy may occur, but the electrocardiogram substantially underestimates the frequency of cardiac hypertrophy compared with that observed with the echocardiogram. Evidence of ischemia or infarction may be observed late in the disease. Most deaths due to hypertension result from myocardial infarction or congestive heart failure. Recent data suggest that some of the myocardial damage may be mediated by aldosterone in the presence of a normal/high salt intake rather than just the increased blood pressure or an increase in angiotensin II levels per se.

1.5.2 Neurologic effects

The neurologic effects of long standing hypertension may be divided into retinal and central nervous system changes. Because the retina is the only tissue in which the arteries and arterioles can be examined directly, repeated ophthalmoscopic examination provides the opportunity to observe the progress of the

vascular effects of hypertension. The Heith-Wagener-Barker classification of the *retinal changes* in hypertension has provided a simple and excellent means for serial evaluation of hypertensives patients. Increasing severity of hypertension is associated with focal spasm and progressive general narrowing of the arterioles, as well as the appearance of hemorrhages, exudates, and papilledema. The retinal lesions often produce scotomata, blurred vision, and even blindness, especially when there is papilledema or hemorrhages of the macular area. Hypertensive lesions may develop acutely and, if therapy results in significant reduction of blood pressure, may slow rapid resolution. Rarely, the lesions resolve without therapy. In contrast, retinal arteriolosclerosis results from endothelial and muscular proliferation, and it accurately reflects similar changes in other organs. Sclerotic changes do not develop as rapidly as hypertensives lesions, nor do they regress appreciably with therapy. As a consequence of increased wall thickness and rigidity, sclerotic arterioles distort and compress the veins where the two vessel types cross in their common fibrous sheath, and the reflected light streak from the arterioles is changed by the increased opacity of the vessel wall.

Central nervous system dysfunction also occurs frequently in patients with hypertension. Occipital headaches, most often occurring in the morning, are among the most prominent early symptoms of hypertension. Dizziness, light-headaches, vertigo, tinnitus, and dimmed vision or syncope may also be observed, but the more serious manifestations are due to vascular occlusion, hemorrhages, or encephalopathy. The pathogeneses of the former two disorders are quite different. *Cerebral infarction* is

secondary to the increased atherosclerosis observed in hypertensive patients, whereas *cerebral hemorrhage* is the result of both the elevated arterial pressure and the development of cerebral vascular microaneurysms (Charcot-Bouchard aneurysms). Only age and arterial pressure are known to influence the development of the microaneurysms. Thus, it is not surprising that arterial pressure shows a better association with cerebral hemorrhage than the either cerebral or myocardial infarction.

Hypertensive enchaphalopathy consists of the following symptom complex: severe hypertension, disordered consciousness, increased intracranial pressure, retinopathy with papilledema, and seizures. The pathogenesis is uncertain but is probably not related to arteriolar spasm re cerebral edema. Focal neurologic signs are in frequent and, if present, suggest that infarction, hemorrhage, or transient ischemic attacks are more likely diagnoses. Although some investigators have suggested that prompt lowering of arterial pressure in these patients may adversely affect cerebral blood flow, most studies indicate that this is not the case.

1.5.3 Effects on the kidneys

Arteriosclerotic lesions of the afferent and efferent arterioles and the glomerular capillary tufts are the most common renal vascular lesions in hypertension and result in a decreased glomerular filtration rate and tubular dysfunction. Proteinuria and microscopic hematuria occur because of glomerular lesions, and approxiamtely 10% of the deaths caused by hypertension result from renal failure. Blood loss in hypertension occurs not only from renal lesions; epistaxis, hemoptysis, and,

metrorhagia also occur frequently in these patients.

Table 4: Complication of hypertension

Hypertensive	Atherosclerotic
Accelerated-malignant hypertension (grades III and IV retinopathy)	Cerebral thrombosis
	Myocardial infarction
Encephalopathy	Coronary artery disease
Cerebral hemorrhage	Claudication syndrome
Left ventricular hypertrophy	
Congestive heart failure	
Renal insufficiency	
Aortic dissection	

1.6 Definition and classification of hypertension[1,10,11]

The continuous relationship between the level of blood pressure and the risk of cardiovascular events, and the arbitary nature of the definition of hypertension have contributed to the variation in the definition issued by various national and international authorities and particularly by the Joint National Committee (JNC) in the United State and the World Health Organization and the International Society of Hypertension (WHO-ISH) Guideline Committee. Accordingly, in order to reduce confusion and provide more consistent advice to clinicians around the world, the WHO-ISH Guideline Committee has agrees to adopt in principle the definition and classification provided in JNC VI. This new definition defines the lower limits for the borderline subgroup of mild hypertension in the 1999 WHO-ISH Guidelines. The new

guideline emphasize that the decision to lower the elevated pressure in a particular patients is not base on the level of blood pressure alone on assessment of the total cardiovascular risk in that individual.

Hypertension is therefore defined as a SBP of 140 mm Hg or greater and/or DBP of 90 mm Hg or greater in subjects who are not taking antihypertensive medication. A classification of blood pressure levels in adult over the age of 18 is provided in Table 5. The term "grade 1, 2, and 3" used by JNC VI, since the world "stage" implies progression over time in a way that dose not necessarily apply here. Otherwise, the values chosen and the terms used are those used in JNC VI. The terms "mild", "moderate", and "severe" used in previous versions of the WHO-ISH Guidelines, would correspond to grade 1, 2, and 3 respectively. The widely used term "borderline hypertension" becomes a subgroup within grade 1 hypertension. It must be emphasized that the term "mild hypertension" dose not imply a uniformly benign prognosis, but is used simply to contrast with more severe elevations of blood pressure.

Unlike the earlier guidelines 1993, the 1999 management recommendations do not consider elderly hypertensive patients separately from other patients with primary hypertension. Similarly, treatment of isolated systolic hypertension is not discussed separately. This is because there is now widespread agreement that treating these conditions is at least as effective in reducing cardiovascular risk as is treating classic essential hypertension in middle-aged subjects.

Table 5: Classification of blood pressure for adults aged 18 years and older *[10,11]

Category	Blood pressure, mm Hg		
	Systolic		Diastolic
Optimal	<120	and	<80
Normal	<130	and	<85
High-normal	130-139	or	85-89
Stage 1 hypertension (mild)	140-159	or	90-99
Subgroup: borderline	140-149	or	90-94
Stage 2 hypertension (moderate)	160-179	or	100-109
Stage 3 hypertension (severe)	≥ 180	or	≥ 110
Isolated systolic hypertension	>140	and	<90
Subgroup: borderline	140-149	and	<90

New (1999) WHO-ISH definition and classification of BP levels

* Not taking antihypertensive drugs and not acutely ill. When systolic and diastolic blood pressures fall into different categories, the higher category should be selected to classify the individual's blood pressure status.

Stratification of patients by absolute level of cardiovascular risk

Decisions about the management of patients with hypertension should not be based on the level of blood pressure alone, but also the pressure of other risk factors, concomitant diseases such as diabetes, target-organ damage, and cardiovascular or renal disease, as well as other aspects of the patient's personal, medical, and social situation. To assist with this, guideline provide a simple method by which to estimate the combined effect of several risk factors and conditions on the future absolute risk of major cardiovascular events. The estimates are based on age, gender, smoking, diabetes, cholesterol, history of premature cardiovascular disease, the presence of target-organ

damage, and history of cardiovascular or renal disease. They were calculated from data on the average 10-year risk of cardiovascular death, non-fatal stroke and non-fatal myocardial infarction among participants (average initial age of 60 years; range 45-80 years) in the Framingham Study.

Four categories of absolute cardiovascular risk are defined (low, medium, high, and very high risk). Each category represents a range of absolute disease risks. Within each range, the risk of any one individual will be determined by the severity and number of risk factors presents. So, for example, individual with very high levels of cholesterol or a family history of premature cardiovascular disease in several first-degree relatives will typically have absolute risk levels that are at the higher end of the range provided. Similarly, individuals with other risk factors listed in Table 6 may also have absolute risk levels that are towards the higher end of the range for the category.

How well these estimates predict the absolute risk of cardiovascular disease in Asian, African or other Non-Western populations is uncertain. In those countries in which CHD incidence is relatively low and heart failure or renal disease is more common, the risk factors used to stratify risk in Table 7 should also be useful in stratifying the risk of these diseases.

Low-risk group

The low-risk group includes men below 55 and women below 65 years of age with stage 1 hypertension and no other risk factors. Among individuals in this category,

the risk of major cardiovascular event in the next 10 years is typically less than 15%. The risk will be particularly low in patients with borderline hypertension.

Medium-risk group

This group includes patients with a wide range of blood pressure and risk factor for cardiovascular disease. Some have lower blood pressure and multiple risk factors, whereas others have higher blood pressure and no or few other risk factors. This is the patients group for which the clinical judgement of the responsible doctor will be paramount in determining the need for drug treatment and the time interval before it should be instituted. Among subjects in this group, the risk of a major cardiovascular event over the next 10 years is typically about 15-20%. The risk will be closer to 15% in those patients with stage 1 (mild) hypertension and only one additional risk factor.

High-risk group

This group includes patients with stage 1 or stage 2 hypertension who have three or more risk factors listed in Table 6, diabetes or target-organ damage and patients with stage 3 (severe) hypertension without other risk factors. Among these patients the risk of a major cardiovascular event in following 10 years is typically about 20-30%.

Very high-risk group

Patients with stage 3 hypertension and one or more risk factors and all patients with clinical cardiovascular disease or renal disease (as defined in Table 6) carry the highest risk of cardiovascular events, of the order of 30% or more over 10 years, and thus qualify for the most intensive and rapidly instituted therapeutics regimens.

Table 6: Factors influencing prognosis[11]

Risk Factors For Cardiovascular Diseases	**Target Organ Damage (TOD)**	**Associated Clinical Conditions (ACC)**
I. Used for risk stratification • Levels of systolic and diastolic Blood pressure (Stage 1-3) • Men > 55 years • Women > 65 years • Smoking • Total cholesterol > 6.5 mmol/L (250 mg/dl) • Diabetes • Family history of premature cardiovascular disease II. Other factors adversely influencing prognosis • Reduced HDL cholesterol • Raised LDL cholesterol • Microalbuminuria in diabetes • Impaired glucose tolerance • Obesity • Sedentary lifestyle • Raised fibrinogen • High risk socioeconomic group • High risk ethnic group • High risk geographic region	• Left ventricular hypertrophy (electrocardiogram, echocardiogram, or radiogram) • Proteinuria and/or slight elevation of plasma creatinine concentration 106-177 mmol/L (1.2-2.0 mg/dl) • Ultrasound or radiological evidence of atherosclerotic plaque (carotid, iliac and femoral arteries, aorta) • Generalized or focal narrowing of the retinal arteries	*Cerebrovascular disease* • Ischaemic stroke • Cerebral haemorrhage • Transient ischaemic attack *Heart disease* • Myocardial infarction • Angina pectoris • Coronary revascularisation • Congestive heart failure *Renal disease* • Diabetic nephropathy • Renal failure (plasma creatinine concentraion >177 mmol/l) (>2.0 mg/dl) *Vascular disease* • Dissecting aneurysm • Symptomatic arterial disease Advenced hypertensive retinopathy • Hemorrhage or exudates • Papiiledema

Table 7: Stratifying risk and qualifying prognosis[11]

	Blood pressure (mm Hg)		
Other risk factors & disease history	Stage 1 (mild hypertension) SBP 140-159 or DBP 90-99	Stage 2 (moderate hypertension) SBP 160-179 or DBP 100-109	Stage 3 (severe hypertension) SBP ≥ 180 or DBP ≥ 110
I. no other risk factors	low risk	medium risk	high risk
II. 1-2 risk factors[(1)]	medium risk	medium risk	very high risk
III. 3 or more risk factors or TOD[(2)]	high risk	high risk	very high risk
IV. ACC[(3)]	very high risk	very high risk	very high risk

[(1)] See table 6

[(2)] TOD – target organ damge

[(3)] ACC – associated clinical conditions, including clinical cardiovascular or renal disease (see Table 6)

2. Blood pressure measurement[10-11,14-16,18-19]

Accurate blood pressure (BP) measurement is essential to the reliable assessment of antihypertensive drugs. The casual office or clinic method of measuring BP has been used routinely in clinical trials of antihypertensive agents. The usual, indirect method of measuring blood pressure is with the sphygmomanometer cuff on the patient's arm at the level of the heart. It is important to use a proper size cuff to avoid overestimating the actual pressure when the cuff is too small. It has become common practice to use duplicate or triplicate measurements during a 1- to 4- week placebo period and then again during the treatment periods, although multiple casual BP measurements are not required by the Food and Drug Administration (FDA) and apparently do not offer information different from a single measurement.

Although, it may be practical to streamline data collection as much as possible during clinical antihypertensive drug trials, data reduction also may result in potential deposits in important information about an antihypertensive agent before it is marketed. For example, there is great interest in the duration of an antihypertensive drug's pharmacodynamic activity because once daily dosing has become a sought-after property of most new agents. It is impossible to establish duration of antihypertensive activity accurately with simple, casual measurements. Potential alternatives for assessing antihypertensive efficacy over time include 1) taking frequent casual BP measurements in clinical research units, 2) having patients take doses in outpatient clinics, wait in the facility for peak effects, and return later for trough measurements (peak-trough effects), or 3) use of non-invasive automatic ambulatory BP monitoring after dosing.

Casual (clinic or office) BP determinations

The casual BP measurement is of value in that it is reasonably replicable as long as the conditions in which the measurements are made are similar. However, although the level of arterial pressure as measured at the clinic is an important risk factor in populations, its predictive value in individual patients is poor. This poor predictive power of clinic pressure reading may be due to the multifactorial nature of the pathogenesis of cardiovascular damage. Moreover, clinic blood pressure measurements are often affected by the alerting reaction induced in patients by the doctor's presence, and this reaction causes a rise in blood pressure which may be both large and unpredictable. Also known as the "white-coat effect", this alerting reaction interferes with the evaluation of antihypertensive treatment by clinic readings in two ways. Firstly, due to the associated pressor response, the alerting reaction may cause on overestimates of the initial blood pressure levels. Secondly, it may lead to an underestimate of the reduction in blood pressure achieved with treatment.

Automatic ambulatory monitoring of BP (ABPM)

For the past several years, portable recorders have been used for the study of BP over prolonged periods. This use a portable device with an inflatable cuff, a compressor, an oscillometric or sphygmomanometric guage and an electronic recorder. In order to avoid misuse, it is essential that all operators have an understanding of the normal ranges of ambulatory blood pressure variabilities and usual circadian rhythms. In addition, the operators must be familiar with the equipment and with the calibration procedures. Subjects for ambulatory blood pressure measurement must be capable of coping with and caring for recorder. The conditions of

measurement for the subject should be standardized as far as possible in relation to activity; in particular the arm should be held still during each measurement. The subjects should be asked to keep a diary of activities during the recording period, unless motion-logging, as an objective assessment of activity, is available.

Comparing casual BP measurements with ambulatory BP measurements

In most clinical antihypertensive drug trials, the casual BP measurement is determined with two goals in mind. The first, and more scientific goal, is to calculate the actual reduction of BP in mm Hg after drug administration. A second parameter to be evaluated is "BP control" or the clinical response to the study drug, that is, the number of patients who achieved a particular goal of therapy. Ambulatory blood pressure monitoring offers a number of advantages over clinic readings. For example, automates or semi-automated blood pressure measurements delivered by non-invasive monitors do not elicit an alerting reaction and a rise in blood pressure. Furthermore, ambulatory blood pressure monitoring allows the effectiveness of a given antihypertensive drug to be tested not just in the artificial environment of the physician's office, but under exposure to the variable physical and psychological stimuli in daily life. By using ambulatory monitoring, precise and detailed information can be obtained on the time-course of the blood pressure fall induced by antihypertensive drugs. With this technique the exact time of the real daily life, peak antihypertensive drug effect can be identified and the persistence of the reduction can be followed over 24 hour. A further advantage is that there is no placebo effect to modify the 24-hour average blood pressure. The US Association for the Advancement of Medical Instrumentation (AAMI) and the British Hypertension Society (BHS) recommendation ABPM

that are approved for coverage for five indications: white coat hypertension, apparent resistance to antihypertensive drugs, hypotensive symptoms with antihypertensive medications, episodic hypertension, and autonomic dysfunction. There are two limitations of ambulatory blood pressure monitoring. (1) average hourly values are not reproducible as average 24-hour values, and this varies between different hours. This means that the number of study patients cannot be reduced from the number required. (2) the discontinuous nature of the measurement delivered by ambulatory monitoring dose not allow a precise estimate of the variability in blood pressure. With the distinct features of ABPM from conventional method make this device almost a necessity in antihypertensive clinical trials. These are as follows

1. *Reliable identification on the target population*

Antihypertensive therapeutic effects can be demonstrated only in hypertensive Patients. Thus, their correct identification is of almost importance. Only ABPM allows for the correct diagnosis "hypertension" as there is no white coat effect. ABPM dose so within on measurement day. With home measurement about three days are needed while, with casual clinic measurement, up to three or four months are needed to achieve a similar correct diagnosis. Thus, the use of ABPM will shorten considerably the time necessary to identify suitable patients. There is an ethical reason for the use of ABPM to ensure a correct diagnosis. Patients who are not really hypertensive cannot benefit from antihypertensive treatment but they may be exposed to possible adverse drug reactions, which are not balanced by therapeutic benefit.

2. *Reduction of sample size*

ABPM dose not respond to placebo and is highly reproducible. Thus, the sample size required to show efficacy of an antihypertensive treatment can be reduced markedly. Two studies have shown independently almost identical effects of repeated measurements on the standard deviation of the difference on sample size. Probably, these computations are over-optimistic as one has to allow for losses resulting from drop-outs and technical failures. Nevertheless, a reduction of the required sample size of about 50% seems realistic.

3. *Assessment of non-drug therapies*

The effect of non-drug therapies on lowering arterial pressure lies in the range of 3-6 mm Hg. Such difference have been assumed by many as clinically not relevant. Recent attempts to adjust the data of the Framingham study with regard to regression dilution bias because of casual clinic measurements at baseline indicate strongly that the regression for diastolic pressure and relative risk of stroke is much steeper than had been assumed until then. Thus, a decrease of 5 mm Hg in diastolic pressure, for example, can equal a 75% reduction of the relative risk of stroke.

4. *Assessment of dose-response relationship and duration of drug action*

The proper assessment of the dose-response curve is easier with ABPM. There is less variability, thus smaller sample size and a shorter period of time may suffice. ABPM is a truly elegant way to assess a drug's duration of action and this is not only important for drugs given once daily.

5. Assessment of night-time blood pressure

There are reports that nighttime arterial pressure correlates more closely with target organ damage than daytime pressure. If these observations can be confirmed in prospective studied, arterial pressure control during nighttime will become an important therapeutic objective.

There are concerns among clinician that nighttime arterial pressure could fall too much with antihypertensive treatment so that regional blood flow, especially in patients with arteriosclerosis, is insufficient. Thus, ABPM at nighttime also serves a safety purpose.

A third indication for measuring nighttime pressure is the evaluation of drug given once daily. Drugs with a once-a-day regimen have to demonstrate that there is adequate arterial pressure control during nighttime and especially in the early morning hours before the effect of the next dose is seen.

3. Prognostic Significant of 24-hour Blood Pressure (BP) variable[60-62]

Several studies have shown that various measures of organ damage associated with hypertension correlate to a greater degree with 24-hour average arterial blood pressure than with clinic blood pressure. Many types of information can be obtained by using 24-hour ABPM device, including an individual's true blood pressure level, amplitude of diurnal variation, short-term blood pressure variability and blood pressure load, all of which might have prognostic significance.

Prognostic significance of average 24-hour and daytime blood pressure

Average daytime blood pressure values obtained non-invasively by a semi-automatic measuring device were correlated more closely with the overall end-organ damage in patients with hypertension than clinic blood pressure values. This finding was later confirmed by other investigators who provided the following additional evidence: (1) both the daytime blood pressure and the 24-hour average blood pressure are correlated more closely with end organ damage in hypertensive patients than clinic blood pressure; (2) the close correlation between 24-hour average blood pressure and end-organ damage can be seen when organ damage is measured by a comprehensive score based on patient history and clinical and laboratory examinations, and when different (and sometimes more sensitive) measures of individual end organ damage are considered. Thus, albuminuria, cerebral lacunae, left ventricular hypertrophy, and retinopathy have all shown a greater correlation with 24-hour average values than with clinic values.

Prognostic significance of blood pressure variability

Blood pressure variations over 24-hour are correlated with end-organ damage in hypetensive patients. The greater incidence and severity of end-organ damage was seen in the classes with greater blood pressure variability. Another support was shown by the study in 73 hypertensive patients using intra-arterial ambulatory monitoring. It was found that among the blood pressure readings taken at baseline, the short-term variability (defined as the standard deviation of consecutive half-hourly values during the daytime) was the best predictor of subsequent left ventricular mass. The other significant predictor was an aggregate measure of target-organ damage based on the ECG, chest X-ray, examination of the fundus and the serum creatinine concentration. The variability in blood pressure also predicted aggregate target-organ damage at follow-up, but blood pressure level was not predictor.

Prognostic significance of the diurnal rhythm of blood pressure

Blood pressure usually follows a circadian rhythm with pressure levels higher during the day and lower at night. In most people, blood pressure falls during the night by more than 10%, such people are often referred to as dippers. But there are others (non-dippers) in whom the fall in blood pressure is smaller. The blunted circadian pattern has been reported to be associated with increased prevalence of left ventricular hypertrophy, atherosclerosis and stroke. In addition, a few cross-sectional studies have indicated that target-organ damage is more pronounced in non-dippers than in dippers with comparable clinic blood pressure. It has also been suggested that this difference applies to women but not to men.

Prognostic significance of the daily blood pressure load

A study by White et al. In 30 never previously treated patients with mild to moderate essential hypertension via 24-hour ambulatory BP monitoring indicated that percentage of elevated BP values that includes both the awake and asleep periods is predictive of cardiac target-organ damage involvement. Elevated BP values during the awake hours (>140/90 mm Hg) and sleeping hours (>120/80 mm Hg) were used to calculate the total percentage of abnormal BP values (load) in each patient. It was found that the BP loads were related to left ventricular mass index and left atrial index more strongly than were the mean 24-hour BP values. Moreover, if > 40% of the ambulatory BP values were elevated, the likelihood of increased mass or decreased filling was greater than 61%, whereas if <40% of the BP values were elevated, the incidence of an abnormal cardiac test result decreased to less than 17%.

4. Hydrochlorothiazide[1,14,58-59,63-64]

Hydrochlorothiazide became and for more than 30 years has remained the cornerstone of the thiazide diuretic group and antihypertensive. It is the most widely prescribed drug in this class of diuretics. It is the 3,4-dihydro derivative of chlorothiazide. Its chemical name is 6-chloro-3,4-dihydro-*2H*-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide. Its empirical formula is $C_7H_8ClN_3O_4S_2$.

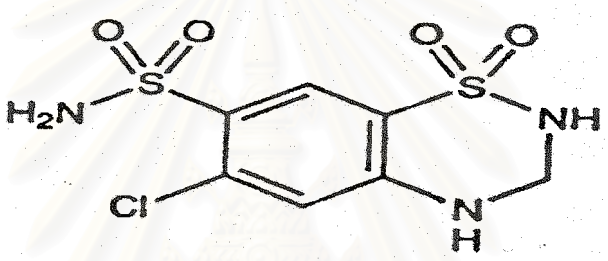

Figure 2: Chemical structure of hydrochlorothiazide[63]

Pharmacologic action and pharmacokinetics[63-64]

Hydrochlorothiazide (HCTZ) diuretics act to inhibit the reabsorption of sodium and chloride in the more distal part of the nephron, resulting in increased urinary excretion of sodium and water. More sodium reaches the distal tubules to stimulate the exchange with potassium, particularly in the presence of an activated renin-angiotensin-aldosterone system. HCTZ may also increase the active excretion of potassium in the distal renal tubule and tendency to reduce urine calcium. HCTZ are rapidly absorbed from the gastrointestinal (GI) tract and seventy-one percent of an oral dose of HCTZ is absorbed. The onset of diuresis is within 2 hours, peaks between 3 and

6 hours, and continues for up 12 to 24 hours. Food may result in a small (15%) decrease in HCTZ efficacy. HCTZ distribution 3.6-7.8 l/kg and protein binding 68%. It is primarily excreted in unchanged form in the urine. HCTZ's pharmacokinetics follow a two-compartment model of elimination (α phase 5 hr, β phase 6 to 15 hr), and the half-life of HCTZ usually 5.6 to 14.8 hours but is prolonged in decompensated heart failure and with renal insufficiency.

Some major differences from the loop diuretics are (1) the longer duration of action, (2) the difference site of action, (3) thiazide are low-ceiling diuretics, flat dose-response curve because the maximal response is reached at a relatively low dosage, and (4) the much decreased capacity of thiazides to work in presence of renal failure (serum creatinine > 2 mg/dl or about 180 μmol/L; glomerular filtration rate [GFR] below 15 to 20 ml/min).

Effects on pathophysiology[63]

1. Effects on hemodynamics

As a consequence of their natriuretic effects, all of the thiazide and thiazide-like diuretics deplete extracellular fluid volume. Patients with edematous states usually experience slow but constant weight losses as long as mobilizable extracellular fluid is present. After peripheral edema clears, it is more difficult to mobilize ascitic and pleural fluid. Depletion of intravascular volume activates counterregulatory mechanisms: increased proximal tubular reabsorption of salt and water, aldosterone stimulation of distal sodium reabsorption and hydrogen and potassium excretion, and antidiuretic hormone-stimulated reabsorption of tubular fluid across the collecting tubule. Collectively, these events have been called the *braking phenomenon*. Nonedematous hypertensive patients will also lose 0.5 to 2.0 kg as a result of

extracellular fluid volume diuresis. The counterregulatory mechanisms discussed earlier will be activated, and homeostasis will be achieved and maintained at a lower body weight. With time, total peripheral resistance will fall. Although the exact mechanism for this chain of events has not been established, possible factors include decreased sensitivity and reactivity of the resistance arterioles to vasoactive humoral agents. Additional possible factors include an effect like calcium channel blocking at the membrane level and reverse autoregulation.

2. Effects on ventricular function and structure

Thiazide diuretics improve ventricular function in patients with congestive heart failure by reducing preload, thereby allowing the ventricle to function in a more efficient range of the Frank-Starling curve. In hypertensive patients, the use of thiazide diuretics alone does decrease the mass of a hypertrophied left ventricle. When thiazide are used as adjuncts to other antihypertensive drugs, especially in severely hypertensive patients who have a component of congestive heart failure, the cardiac silhouette can be reduced on standard chest radiographs and the strain pattern on the electrocardiogram can be reversed.

3. Effects on electrophysiology

The thiazide diuretics have no direct effect on cardiac electrophysiology. Nevertheless, the question of cardiac arrhythmias associated with metabolic changes induced by diuretics remains extremely controversial. Evidence suggests that epinephrine lowers serum potassium concentration, that hypokalemia, per se, can induce and increase the frequency and severity of vnetricular ectopy, and that hypokalemic patients are at greater risk of serious dysrhythmias at the time of myocardial infarction. Caralis et al. found that ventricular ectopy

could be induced only in patients with clinically apparent organic heart disease by history, physical finding, chest radiograph, or electrocardiogram. These findings led to a recommendation that potassium supplement should be reserved for patients with clinical evidence of organic heart disease.

Effects on body fluids, volume status, and eletrolytes[63-66]

-Volume depletion

The most fundamental effect of a diuretic drug is an increase in the output of urine. If fluid intake is restricted such that a net negative balance of water occurs, total extracellular fluid volume will be depleted. This depletion occurs first from the intravascular fluid compartment. Increased oncotic pressure due to concentration of intravascular proteins alters the Starling forces to favor reabsorption of fluid from the interstitial compartment. Therefore, edema fluid will tend to move bask into the intravascular compartment, form which it can be excreted.

Low serum protein concentration, such as that found in the nephrotic syndrome and decompensated cirrhosis of the liver, will provide much less of an oncotic effect and thereby render the transit of fluid out of the interstitial space less effective. As long as the diuretic remains effective in this clinical setting, intravascular volume may become depleted, and renal blood flow and glomerular filtration rate may decrease; thus, the patient may become more susceptible to symptomatic orthostatic hypotension.

- Hypokalemia

The effects of thiazide diuretics on serum electrolyte are well known. Hypokalemia, especially in non-edematous states, is a direct function of diuretic dose. This

quality is of great clinical importance because of the need to use only the lowest effective dose of the diuretic so that the possibility of hypokalemia is minimized. The risk of hypokalemia can be further minimized by moderate dietary sodium restriction to about 70 to 100 mmol/day and by encouraging consumption of fresh potassium-rich fruits and vegetables. Routine potassium supplement or use of potassium-sparing diuretic drugs in patients with uncomplicated hypertension is probably not warranted.

- *Hyponatremia*

Hyponatremia due to thiazide diuretics is uncommon but of great clinical importance because it is potentially disabling or life-threatening. Because all thiazides interfere with the clearance of free water, patients who take these drugs and consume large quantities of water may develop significant dilutional hyponatremia within a few days. Patients taking a thiazide-type diuretic should be warned that they should contact their physician immediately if they experience headache, nausea, or vomiting. A serum sodium determination should be made at that time.

- *Hypercalcemia*

Serum calcium levels are almost invariably increased slightly by treatment with thiazide diuretics. A purely hypothetical explanation for this phenomenon is that, by depleting the body of excess salt and water, diuretics turn off the secretion of the hypothalamic natriuretic hormone, thereby permitting a corrective shift of intracellular to extracellular calcium. A few patients treated with thiazide diuretic develop calcium levels substantially above the normal

range. The latter benefit could be explained by a beneficial side effect of thiazide diuretics whereby calcium is shifted into bone, thus increasing bone density.[63,67]

- Magnesium and Zinc depletion

Prolonged treatment with thiazide-type diuretics also can deplete body stores of magnesium. Because serum magnesium levels reflect intracellular magnesium contents so poorly, it is difficult to perform definitive studies that determine the importance of this phenomenon. Magnesium and potassium depletion have been proposed as determinants of diuretics associated ventricular ectopic activity, but this theory is unproved. Zinc also may be lost in the urine during chronic thiazide diuretic treatment. This loss is more likely to take place in patients with edema than in those with hypertension. The clinical importance of zinc loss remains unknown. There is an unsubstantiated suggestion that zinc loss is associated with sexual dysfunction.

Endocrine and metabolic effect

All thiazide diuretics activate the endocrine counterregulatory hormonal systems. This activation includes the release of renin, angiotensin, aldosterone, antidiuretic hormone, and norepinephrine. Serum concentration of uric acid predictably will increase by 1 to 1.5 mg/dl, and this elevation will be maintained for the duration of thiazide diuretic therapy. Carbohydrate metabolism may be impaired in some patients. When thiazide administration is terminated, plasma glucose levels tend to return quickly to baseline. These mechanism are largely related to hypokalemia but also may be partly due to decreased sensitivity of islet cells to catecholamines. It is also possible that diuretics have direct effect on pancreatic β-cell. The use of thiazide diuretics in patients with diabetes mellitus has become highly controversial. There is evidence that HCTZ

is associated with a decrease in insulin sensitivity in contrast with most other antihypertensive drugs. On the other hand, because overall data from many more recent studies show that cardiovascular mortality was decreased on therapy with lower dosage of a thiazide diuretic, the Joint National Committee recently has recommended that thiazides and β-blockers be the first-line antihypertensive agents of choice for treating hypertenstion in general. However, these studies generally exclude insulin-dependent or unstable diabetics.

The effect of thiazide diuretics on plasma lipids remain highly controversial. It is clear that thiazide diuretics elevate total serum cholesterol levels initially perhaps by elevating the concentration of low-density lipoprotein (LDL) cholesterol. Restriction of dietary intake of fat may prevent diuretic-associated increases in serum cholesterol. Some data suggest that cholesterol levels return to baseline values after 6 months diuretic therapy. However, it is possible that a placebo-controlled baseline value may become lower with time because of regression toward the mean. Therefore, a lipid-elevating effect of thiazides might still be present. Any association of these diuretic-induced, elevated lipid levels with an increased risk of coronary heart disease is inferential and has not been proved.

Effects on renal hemodynamics

Because thaizide diuretics deplete intravascular volume, they predictably reduce renal blood flow and glomerular filtration rate slightly. This reduction reflected by a small increase in the serum concentration of urea nitrogen (2 to 5 mg/dl is the usual normal range) and a trivial increase in serum creatinine concentration. In general, thiazide and thiazide-like diuretics tend to lose their antihypertensive and diuretic efficacy as glomerular filtration rate declines.

Clinical use[63-64,68]

- *Dosages and indications*

In hypertension, thiazide diuretics still appear to be the initial agent of choice, especially in the elderly and in black patients. Lower doses with fewer biochemical alterations provide full antihypertensive effects, as shown in several large trials. Higher doses are marginally more effective, with greater risks of undesirable side effects. A Veterans Administration study demonstrated that dose of HCTZ as low as 12.5 mg daily were effective in treating patients with mild to moderate hypertension The response depends in part on the age and race of the patient and probably also on the sodium intake. HCTZ was most effective in older blacks and least effective in younger whites. Increasing the dose of HCTZ up to a maximum of 200 mg daily may improve the response, but the risk of metabolic side effects is unacceptably high, so combination therapy becomes preferable rather than increasing the dose beyond 25 mg daily.

In congestive heart failure, higher doses are justified (50 to 100 mg hydrochlorothiazide daily are probably ceiling doses), while watching the serum potassium. Considerable advantage can result from combining a loop diuretic with a thiazide. Specifically, the thiazide block the nephron sites at which hypertrophy occurs during long term loop diuretic therapy.

- *Contraindications*

These include hypersensitivity, renal insufficiency, hypokalemia, ventricular arrhythmias, and co-therapy with proarrhythmic drugs. In hypokalemia (including early AMI), thiazide diuretics may precipitate arrthythmias. Relative contraindications include pregnancy

hypertension, because of the risk of a decreased blood volume; thiazides can cross the placental barrier with risk of neonatal jaundice. In mild renal impairment, the GFR may fall further as thiazides decrease the blood volume.

- *Side effects*

Besides the "wrong way" metabolic side effects seen with high doses such as hypokalemia, hyponatremia, hyperuricemia, increased insulin resistance, and increased blood triglyceride and cholesterol levels, thiazide diuretics rarely cause sulfonamide-type immune side effects including intrahepatic jaundice, pancreatitis, blood dyscrasias, angiitis, pneumonitis, and interstitial nephritis. Impotence is newly emphasized. HCTZ is associated occasionally with phototoxic skin reaction. Patients characteristically have a diffuse maculopapular rash in sun-exposed areas. The rash disappears with discontinuation of HCTZ.

- *Drug interactions*

Steroids may cause salt retention to antagonize the action of thiazide diuretics. Indomethacin and other NSAIDs blunt the response to thiazide diuretics. Antiarrhythmics that prolong the QT-interval, such as class IA or III agents including sotalol, may precipitate torsades de points in the presence of diuretic-induced hypokalemia. The nephrotoxic effects of certain antibiotics, such as the aminoglycosides, may be potentiated by diuretics. Probenecid (for the therapy of gout) and lithium (for mania) may block thiazide effects by interfering with thiazide excretion into urine. Thiazide diuretics also interact with lithium by impairing renal clearance; thus there is a risk of lithium toxicity

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- *Ethanol/nutrition/herb interaction*

Food : Hydrochlorothiazide peak serum levels may be decreased if taken with food. This product may deplete potassium, sodium, and magnesium.

Herb/nutraceutical: Avoid dong quai if using for hypertension (has estrogenic Activity). Dong quai may also cause photosensitization. Avoid ephedra, ginseng, yohimbe (may worsen hypertension. Avoid garlic (may have increased antihypertensive effect).

- *Monitoring parameters*

Assess weight, I&O reports daily to determine fluid loss; blood pressure, serum electrolytes, BUN, creatinine

- *Test interaction*

↑ creatine phosphokinese (CPK), ammonia, amylase, calcium, chloride, cholesterol, glucose, ↑ acid, ↓ chloride, magnesium, potassium, sodium, Tyramine and phentolamine tests, histamine tests for pheochromocytoma.

- *Pregnancy/ breast-feeding precautions*

Consult prescriber if breast-feeding.

5. Calcium carbonate[59,68]

Calcium carbonate is the most common type of calcium supplement.

Pharmacologic action and pharmacokinetics

As dietary supplement, used to prevent or treat negative calcium balance; in osteoporosis, it helps to prevent or decrease the rate of bone loss. The calcium in calcium salts moderates nerve and muscle performance and allows normal cardiac function. Also used to treat hyperphophatemia in patients with advances renal insufficiency by combining with dietary phosphate to form insoluble calcium phosphate, which is excreted in feces. Calcium salts as antacids neutralize gastric acidity resulting in increased gastric an duodenal bulb pH; they additionally inhibit proteolytic activity of peptic if the pH is increased >4 and increase lower esophageal sphincter tone.

Calcium carbonate absorbed from gastrointestinal (GI) tract requires vitamin D; calcium is absorbed in soluble, ionized form; solubility of calcium is increased in an acid environment, especially acidic foods such as citrus juice or fruit. The National Institutes of Health (NIH) consensus statement on optimal calcium intake recommends taking no more than 500 milligram (mg) elemental calcium. Calcium can distribute across the placenta; appear in breast milk. It is mainly eliminate in feces as unabsorbed calcium with 20% eliminated by the kidney.

Cardiovascular effects of calcium[59]

1. Calcium in systemic hypertension

Calcium metabolism is linked closely to the regulation of systemic blood pressure, and calcium supplement has been proposed as a treatment for systemic hypertension.

Increased concentrations of free calcium bound within the cytosol of vascular smooth-muscle cells are thought to be responsible for the increased contractility of vessels in hypertension. Hypertension can develop if a general increase in systemic arteriolar tone leads to a rise in peripheral flow resistance. Furthermore, with progressive elevation of calcium, the structural integrity of the arterial and arteriolar walls is destroyed. Thus, in various animal models, calcium overload initiates lesions of an arteriosclerotic character. The increased concentrations of free calcium within the vascular smooth-muscle cells could be secondary to alterations in calcium entry, binding, or extrusion from the cells. Studies on human cells have shown changes related to all three of these mechanisms.

Beyond the probability that an increased intracellular calcium is involved in the pathogenesis of hypertension, there are other observed relationships between calcium and hypertension. These include the relationship between serum calcium levels and blood pressure, the effects of dietary and supplement calcium on blood pressure, and the renal excretion of calcium and serum parathyroid hormone (PTH) levels in patients with hypertension.

2. *Serum calcium and hypertension*

Hypertension is more common in the presence of hypercalcemia, and in many but not all studies, there appears to be a direct relationship between the total serum calcium level and blood pressure. However, the relationship between serum ionized calcium and blood pressure does not appear to be strong. Nevertheless, there is enough data to suggest a vasoconstrictive effect of increasing extracellular calcium levels presumably by a stimulation of catecholamine release.

3. *Increased renal excretion of calcium*

Compared with normotensive subjects, hypertensive individuals excrete more calcium both under basal circumstances and during a calcium infusion. This may be due to the increase in calcium excretion known to occur following intravascular volume expansion with the resultant rise in sodium excretion. Alternatively, it may be secondary to a decreased binding of calcium to kidney cells. Whatever the precise mechanism, it is known that patients with volume-expansion forms of hypertension excrete calcium in excess.

4. *Increased levels of parathyroid hormone (PTH)*

Hypertensive patients tend to have increased levels of plasma PTH, most likely as a homeostatic response to their urinary calcium leak. Although not nearly as elevated as those seen with primary parathyroidism, these elevated PTH levels could exert a pressor effect and thereby cause or contribute to the hypertension of volume-expanded states.

Clinical use

- *Dosages and indication*

Calcium carbonate as an antacid, and treatment and prevention of calcium deficiency or hyperphosphatemia (e.g. osteoporosis, osteomalacia, mill/moderate renal insufficiency, hypoparathyroidism, postmenopausal osteoporosis, rickets); has been used to bind phosphate.

Hypocalcemia (dose depends on clinical condition and serum calcium levels):

Dose expressed in mg of elemental calcium

Neonated: 50-150 mg/kg/day in 4-6 divided doses; not to exceed 1 g/day

Children: 45-65 mg/kg/day in 4 divided doses

Adults: 1-2 g or more/day in 3-4 divided doses.

Adults:

Antacid: Dosage based on acid-neutralizing capacity of specific product; generally, 1-2 tablets or 5-10 ml every 2 hours; maximum: 7,000 mg calcium carbonate per 24 hours; specific product labeling should be consulted.

Dietary supplement: The American Heart Association (AHA) publishes these recommendations for adequate daily calcium intake[46]:

- 200 mg for infants from birth to 6 months and 270 mg for ages 6 months to 1 years old.
- 500 mg for children ages 1-3 and 800 mg for ages 4-8.
- 1,300 mg for children ages 9-18.
- 1,000 mg for adult ages 19-50 and 1,200 mg for ages 51 and older.
- 1,300 mg for women who are pregnant and under age 19 and 1,000 mg for pregnant women ages 19-50.

- *Contraindication*

Don't take calcium if you have hypercalcemia, renal calculi, hypophosphatemia

- *Side effects*

People who take calcium supplements may experience constipation, acid rebound, flatulence and headache. Serious side effects include confusion, muscle or bone pain, nausea, vomiting and slow or irregular heart beat.

- *Drug interaction*

Calcium carbonate (and possibly other salts) may decrease T_4 absorption, tetracycline, atenolol (and potentially other beta-blocker), iron, quinolone antibiotics, alendronate, sodium fluoride, and zinc absorption is significant decreased; space administration time. Thiazide diuretics can cause milk-alkali syndrome and hypercalcemia.

- *Ethanol/nutrition/herb interactions*

Food may increase calcium absorption. Calcium may decrease iron absorption. Bran, foods high in oxalates, or whole grain cereals may decrease calcium absorption

- *Test interaction*

↑ calcium; ↓ magnesium

- *Pregnancy implications*

Available evidence suggests safe use during pregnancy and breast-feeding

CHAPTER III

MATERIALS AND METHODS

The study was conducted from June 2001 to JUNE 2002 at King Chulalongkorn Memorial Hospital, Bangkok, Thailand.

Materials

1. Drugs

   - Hydrochlorothiazide (Dichlotride®) 25 mg tablets Lot No. 501022, Mfg. Date. 9 March 2001.

   - Calcium carbonate (Chalkcap-1000®) 1000 mg tablets equivalent to calcium 400 mg Lot No. 10107326 Mfg. Date. 20 July 2001.

2. Instruments

   - Mercury Sphygmomanometer

   - 24-hour Ambulatory blood pressure monitoring machine (Figure 3) (QuietTrak™, Welch Allyn Tycos, U.S.A., Blood pressure measuring devices: recommendations of the European Society of Hypertension)

Patients

This study was designed as a randomized, double-blind, run-in placebo, cross over trial to assess the single and combined effects of calcium and hydrochlorothiazide on 24-hour blood pressure and to describe the relationship between 24-urinary excretion of sodium and calcium on 24-hour blood pressure. The study was approved by the ethics committee of King Chulalongkorn Memorial Hospital. All patients entering the study gave their informed consent. The patients with

mild to moderate primary hypertension were recruited for this study based on the following criteria:

Inclusion criteria

- The patients were men or women with an aged of 18 years old or older
- Primary hypertensive with the office sitting systolic blood pressure (SBP) in the range of 140-179 mm Hg and/or diastolic blood pressure (DBP) in the range of 90-109 mm Hg at the end of an initial 2 weeks placebo run-in period (at baseline) or after the withdrawal of antihypertensive drugs and/or calcium supplements daily intake and placebo run-in for at least 5 times of half-life
- Mean 24-hour ambulatory blood pressure (mean 24-hr ABP) showed that SBP $\geq$ 135 mm Hg and/or DBP $\geq$ 85 mm Hg after 2 weeks placebo run-in and washout period able to recruited
- The patients were willing to cooperate in the study and signed the consent form

Exclusion criteria

- Secondary hypertension of any etiologies
- Having chronic diseases such as other cardiovascular diseases (e.g. congestive heart failure, myocardial infarction, angina pectoris)
- Having a history of hypertensive encephalopathy or cerebrovascular accident
- Significantly impaired renal function (serum creatinine >3.0 mg/dl)
- Significantly impaired liver function (AST and/or ALT > 3 times of upper limit)
- Hypersensitivity to sulfonamide or hydrochlorothiazide or calcium carbonate

- Having diseases associated with parathyroid hormone, adrenal insufficiency, malignancy, hypercalcemia (serum calcium > 12 mg/dl)
- Concomittant therapy with drugs that interfere with the antihypertensive effects such as corticosteroid, non-steroidal antiinflamatory drugs (NSAIDs), etc. were not allowed to this study
- Pregnancy or lactation

Methods

1. Study design

After a washout and placebo run-in period from any previous antihypertensive therapy and calcium supplement for 2 weeks. At visits after 2 weeks of placebo, office sitting blood pressure (OBP) were measured by mercury sphygmomanometer, 24-hour blood pressure were monitored by using 24-hour ambulatory blood pressure monitoring (ABPM) machine, blood samples for routine laboratory assessment and collection of 24-hour urine excretion. The patients were eligible for this study if their mean office blood pressure measured in triplicate by mercury sphygmomanometer after sitting quietly for 5 minutes systolic blood pressure (SBP) was 140-179 mm Hg and/or diastolic blood pressure (DBP) was 90-109 mm Hg. A further eligibility criterion was a mean 24-hour ambulatory blood pressure (mean 24-hr ABP) was 24-hour systolic blood pressure $\geq$ 135 mm Hg and/or 24-hour diastolic blood pressure $\geq$ 85 mm Hg.

Patients were randomly assigned to receive hydrochlorothiazide 25 mg once daily before breakfast combined placebo of calcium carbonate 1000 mg twice daily

before breakfast and bedtime (group I) or calcium carbonate 1000 mg (equivalent to calcium 400 mg) twice daily before breakfast and bedtime combined placebo of hydrochlorothiazide once daily before breakfast (group II) for 4 weeks. Office blood pressure, 24-hour ABPM were evaluated, blood sample to investigate sodium, calcium, creatinine and collected 24-hour urine excretion.

Patients in group I would be prescribed to receive calcium carbonate 1000 mg (equivalent to calcium 400 mg) twice daily before breakfast and bedtime whereas patients in group II would be added hydrochlorothiazide 25 mg once daily before breakfast for another 4 weeks treatment period. Office blood pressure, 24-hour ABPM, blood sample for routine laboratory assessment and collection of 24-hour urine excretion were performed after that. The patients were request to record theirs activities while the monitoring was going on. Study flow chart is shown in Figure 4.

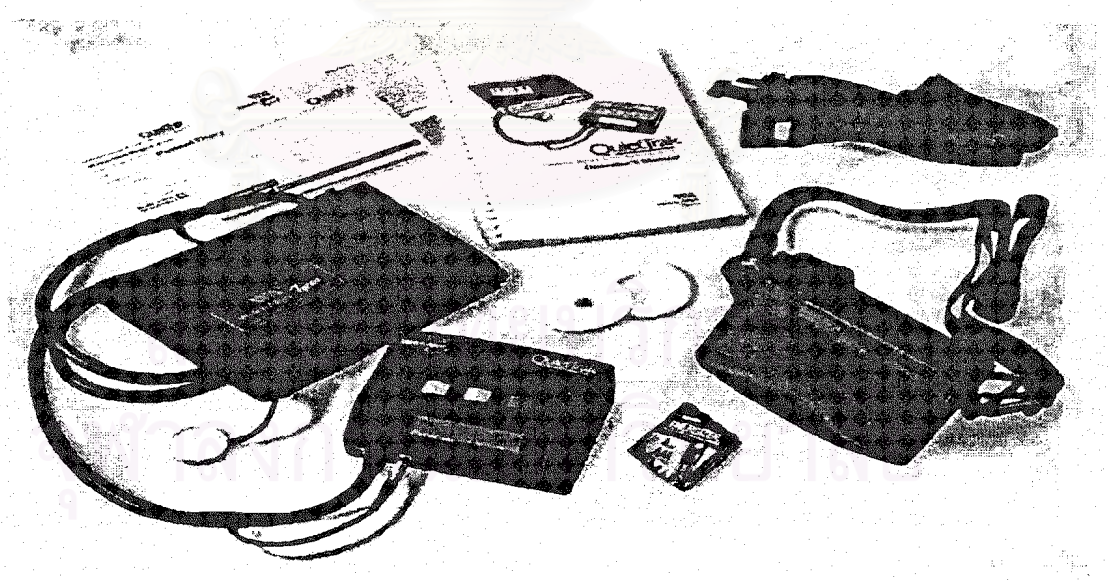

Figure 3: 24-hour Ambulatory blood pressure monitoring machine

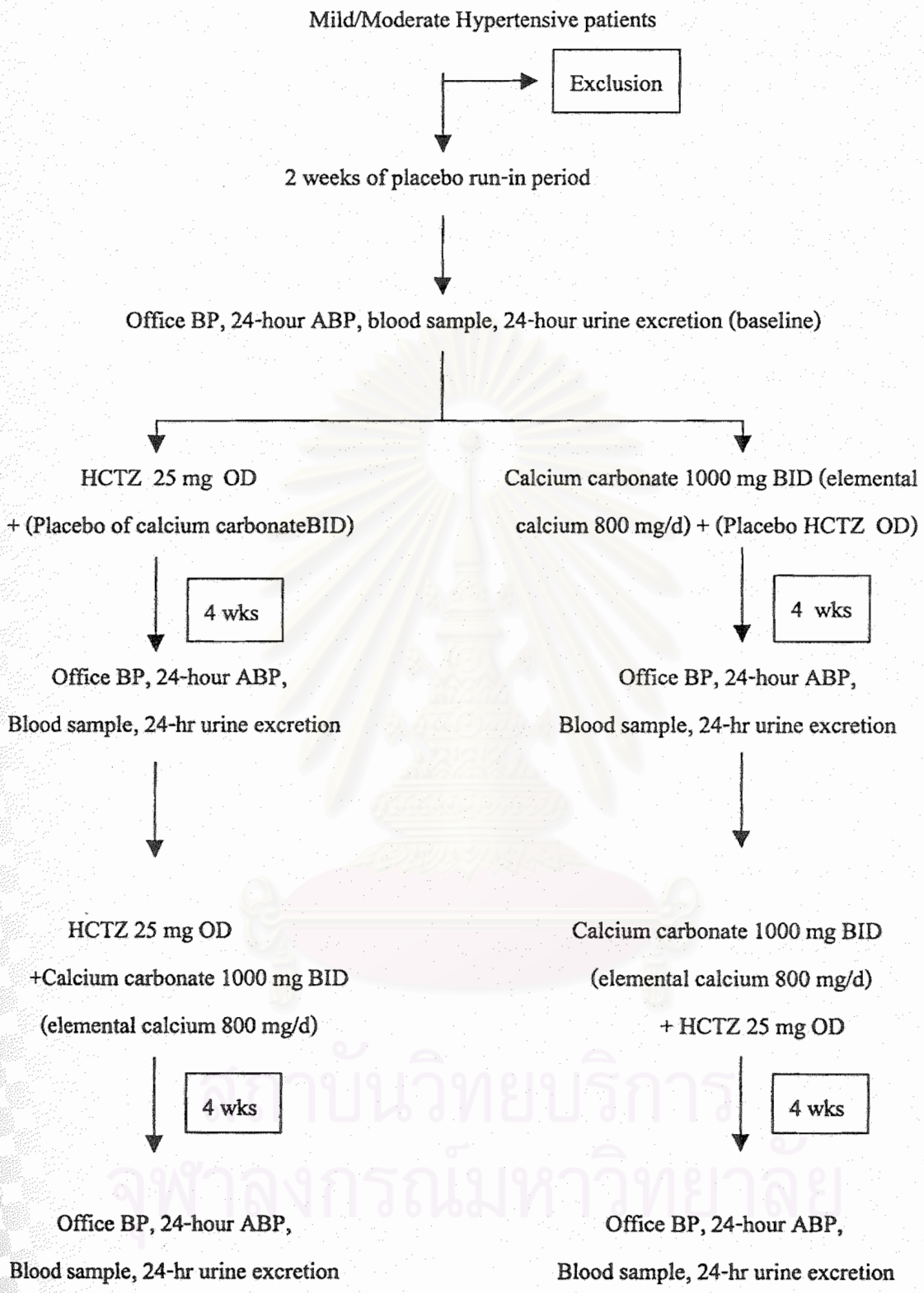

Figure 4: The study flow chart

2. Procedures

2.1 Office blood pressure measurement

Sitting SBP and DBP were measured with a mercury sphygmomanometer (korotkoff I and V for SBP and DBP, respectively) on the left arm after patients had been resting in the sitting position for 5 minutes. Three consecutive BP measurement and heart rate were recorded.

2.2 24-hour ambulatory blood pressure measurement

24-hour ambulatory blood pressure and HR were measured with a portable, non-invasive, fully automatic BP recorder which can be used auscultatory method (QuietTrak™, Welch Allyn Tycos, U.S.A.). The adult cuff (range: 18-32 cm.) was applied to the left arm of each patient. The device was programmed to provide a blood pressure and heart rate measurement every 30 minutes intervals for the day-time (06.00 a.m.-09.00 p.m.) and every 60 minutes intervals for the night-time (09.00 p.m.-06.00 a.m.). Patients were allowed to have their normal daily activities after they left the hospital. However, they were instructed to remain motionless each time a reading was taken.

2.3 24-hour urine collection

24-hour urine excretion were collected before the patients went to hospital each time for 1 day. They were instructed to collect 24-hour urine completely.

3. Data analysis

3.1 Office blood pressure measurement

The average of three measurements of BP and HR was used for further analysis. The mean arterial pressure (MAP) was calculated as DBP plus 1/3 of the difference between SBP and DBP (SBP-DBP).

3.2 24-hour ambulatory blood pressure measurement

BP was detected by auscultatory method. Raw data of ambulatory BP and HR were transferred to a computer program. Systolic BP reading >250 or <60 mm Hg or systolic change > 150 mm Hg, diastolic BP reading >160 or <30 mm Hg or diastolic change > 100 mm Hg, and pulse pressure (SBP-DBP) > 150 or < 10 mm Hg were rejected. And when actual values differ by 60 mm Hg or more from each pre-measurement value within 1 hour, the data for the corresponding patient are picked up and individually examined.

Mean values of SBP, DBP, MAP, and HR were calculated separately for each hour, for the whole 24-hour, during day-time and during night-time. Mean hourly values were derived from the average of 2 reading obtained in each hour, such as the value at 08.00 a.m. and 08.30 a.m. were used for the calculation of BP value at 08.00 a.m., day-time and night-time periods were defined as time between 06.00 a.m.- 09.00 p.m. and 09.00 p.m.-06.00 a.m., respectively.

3.3 Responder and normalized

Responders were defined as patients whose sitting office BP or 24- hour ambulatory BP were reduction $\geq$ 10% from baseline.

Normalized were defined as patients whose sitting office SBP/DBP <140/90 mm Hg or 24-hour ambulatory SBP/DBP $\leq$130/80 mm Hg at the end of the test treatment.

3.4 Inverted dipper, non-dipper, dipper, and extreme dipper

Inverted dipper were defined as those patients who had nocturnal increase of BP, whereas whose night-time BP reduction less than 10% were define as non-dipper. Dipper were defined as those patients who had the reduction in night-time BP between 10% and 20% if nocturnal BP fall more than 20% were define extreme dipper.

3.5 BP loads

BP loads were BP values that were higher than 140 or 120 mm Hg for SBP and 90 or 80 mm Hg for DBP during day-time and night-time, respectively. In addition, BP loads were expressed as the frequency or percentage.

3.6 Determine FENa and $FECal_i$ of 24-hour urine excretion

FENa (%) and $FECal_i$ (%) were calculated from following calculation:

$$\text{FENa (\%) and } FECal_i \text{ (\%)} = \frac{\text{Urine (Na/Cal) x Scr}}{\text{Serum (Na/Cal) x Urine Cr}} \times 100$$

4. Statistical analysis

4.1 Result are presented as mean ± SD

4.2 The office BP, 24-hour ABP measurements and 24-hour urine excretion of sodium and calcium before and after treatment with HCTZ 25 mg OD combine placebo of calcium carbonate and calcium carbonate 1000 mg BID combine placebo of HCTZ in cross over design and antihypertensive effects of HCTZ 25 mg combine calcium carbonate 1000 mg BID were compare by using repeated measures analysis of variance (repeated measures ANOVA) and then followed by the Bonferroni correction to calculate the significance of pairwise differences (SPSS 10.01 program).

CHAPTER IV

RESULTS AND DISCUSSION

1. Hypertensive patients

From June 2001 to June 2002, there were total of thirty-seven patients who met the screening criteria for eligibility and entered the placebo run-in period at the out patient department, King Chulalongkorn Memorial Hospital. Eight patients were excluded due to several reasons i.e., seven patients were diagnosed to be white coat hypertension (when we closely monitored with ambulatory blood pressure monitoring device (ABPM), their mean 24-hour SBP were less than 135 mm Hg and DBP were less than 85 mm Hg, while one patient was excluded from this trial because of hypersensitivity with hydrochlorothiazide (HCTZ). At the end of placebo run-in period, only twenty-nine patients with mean 24-hour SBP $\geq$ 135 mm Hg and/or DBP $\geq$ 85 mm Hg measured by ABPM were recruited in this study.

They were allocated randomly into the two regimens of the study therapy, Group 1 was assigned to receive HCTZ 25 mg once daily combined with placebo of calcium carbonate ($CaCO_3$) 1 gm twice daily and group 2 was assigned to receive $CaCO_3$ 1 gm twice daily combined with placebo of HCTZ 25 mg once daily. During the study, four patients were dropped out from the study due to loss of follow up for 1 time. Finally, there were twenty-five patients who could complete this study and their data only were used for statistical analysis (Figure 5).

Demographic data

Characteristics at baseline of the twenty-five patients who enrolled in the study were summarized in Table 8. Six males and nineteen females, with an average age of 61.8 $\pm$ 9.5 years

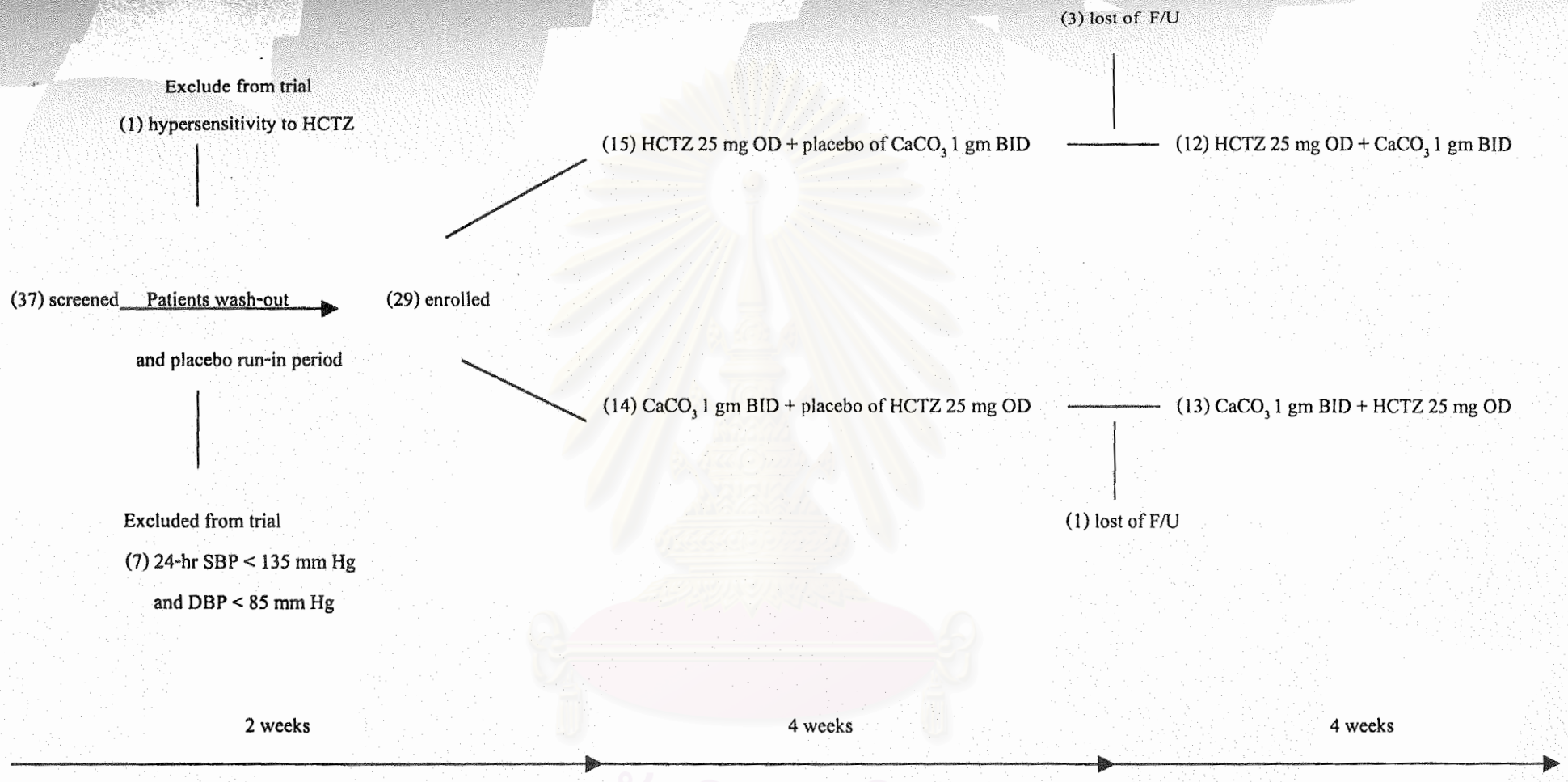

Figure 5: Study flow chart of treatment

Table 8: Demographic data of the subjects at baseline

No. of subjects	25
Sex (no.)	
Male	6
Female	19
Age (years)	
Mean ± SD	61.8 ± 9.5
Range	42.0-81.0
Weight (kg.)	
Mean ± SD	61.4 ± 10.7
Range	31.2-78.0
Height (cm.)	
Mean ± SD	157.6 ± 6.2
Range	148.0-170.0
BMI (kg/m^2)*	
Mean ± SD	24.6 ± 3.7
Range	14.3-32.9
Duration of hypertension (years)	
Mean ± SD	4.8 ± 4.4
Range	0.0-20.0
Cigarettes smoking (no.)	2
Alcoholic (no.)	2
Caffeine drinking (no.)	13
Milk drinking (no.)	10
Previous medication (no.)	
No medication	2
1 medication	8
2 medications	13
3 medications	2

* BMI: body mass index = $\frac{\text{weight}}{(\text{height})^2}$

(range 42-81 years). The average weight, height, and BMI values (mean ± SD) were 61.4 ± 10.7 kg., 157.6 ± 6.2 cm., and 24.6 ± 3.7 kg/m^2, respectively. Duration of hypertension 4.8 ± 4.4 years (range 0-20 years). Two patients currently smoked cigarettes and two patients drank alcohol for social life. In their daily life, thirteen patients drank caffeine 1 cup per day and ten patients drank milk or soymilk 1 cup per day.

Laboratory data at the end of the placebo run-in period or at baseline were shown in Table 9. Majority of these patients had normal levels of laboratory data. Nine patients showed high cholesterol levels (>220 mg/dl), while seven patients showed high triglyceride levels (>155 mg/dl), among them, three patients had both high levels of cholesterol and triglyceride. Three patients showed hyperglycemia (>110 mg/dl), while one patient showed hyperuricemia (>7.0 mg/dl). Three patients showed high levels of liver function test, but not more than two times of the normal ranges. Three patients showed high serum creatinine (>1.2 mg/dl). However, the electrolyte levels of all subjects were in the normal ranges. The demographic and laboratory data of each patient were demonstrated in Appendix A and B, respectively.

2. Blood pressure data of the patients at baseline

Office blood pressure (OBP) at the screening visit and after placebo run-in period were illustrated in Appendix C. Blood pressure after taking placebo was used as the baseline level for comparing the drug effects. Two patients had never been treated for their hypertension while twenty-three of them had been administrated with antihypertensive drug either monotherapy or combination therapy before they entered this trial. There were only little difference in blood pressure between screening visit and after placebo run-in in new onset patients.In treated patients,

Table 9: Laboratory data of the subjects at baseline (n=25)

Test (normal range)[a]	Mean ± SD	Range
FPG (60-110 mg/dl)	98.80 ± 11.09	86.00 - 137.00
Cholesterol (150-220 mg/dl)	213.40 ± 31.01	166.00 - 290.00
Triglyceride (40-155 mg/dl)	137.40 ± 74.51	63.00 - 346.00
HDL (50-100 mg/dl)	53.84 ± 18.72	29.00 - 126.00
LDL (130-159 mg/dl)	132.20 ± 28.54	79.00 - 204.00
BUN (5-20 mg/dl)	14.28 ± 2.97	9.00 - 20.00
SCr (0.5-1.2 mg/dl)	0.97 ± 0.22	0.60 - 1.40
Sodium (135-150 mEq/l)	140.72 ± 2.51	135.00 - 145.00
Calcium (9-11 mg/dl)	9.49 ± 0.40	8.60 - 10.40
Potassium (3.5-5.0 mEq/l)	3.94 ± 0.43	3.50 - 5.10
Phosphate (2.5-4.8 mg/dl)	3.45 ± 0.64	2.30 - 4.80
Albumin (3.8-5.0 g/dl)	4.60 ± 0.33	4.10 - 5.50
SGOT (0-38 U/l)	24.72 ± 10.40	12.00 - 47.00
SGPT (0-38 U/l)	27.28 ± 14.39	6.00 - 55.00
Uric acid (2.0-7.0 mg/dl)	3.97 ± 1.17	2.70 - 7.30

FPG = fasting plasma glucose

HDL = High density lipoprotein

LDL = Low density lipoprotein

BUN = blood urea nitrogen

SCr = serum creatinine

SGOT = serum glutamic oxaloacetic transaminase

SGPT = serum glutamic pyruvic transaminase

[a] = normal range at King Chulalongkorn Memorial Hospital

none of them showed state of severe hypertension (SBP ≥ 180 and/or DBP ≥ 110 mm Hg) after placebo run-in.

Some benefits of ambulatory BP measurement over the standard clinic or office blood pressure measurement in a clinic therapeutic trial have been well established[16-18]. First, it is not substantially affected by the administration of placebo over several weeks. This means that when ambulatory blood pressure is used to determine the efficacy of an antihypertensive drug, a placebo group can be avoided, reducing the study size. Second, it also avoids the error arising from the white-coat effect. Thus, white-coat hypertensive patients could be identified and excluded from the antihypertensive drug trial with 24-hour ABP measurement. Third, 24-hour mean blood pressure is more reproducible than clinic blood pressure.

Table 10 presents blood pressure at the screening visit and at baseline by both office blood pressure and 24-hour ABP measurement, more details were demonstrated in Appendix D. The mean office blood pressure at screening visit was 144 ± 9.39 / 86 ± 6.53 mm Hg, while at baseline the mean office blood pressure was 154 ± 14.00 / 95 ± 9.29 mm Hg. The mean 24-hour blood pressure was 141 ± 12.09 / 92 ± 11.55 mm Hg, the mean day-time blood pressure was 143 ± 12.51 / 93 ± 12.46 mm Hg, and the mean night-time or during sleep was 135 ± 12.59 / 86 ± 14.15 mm Hg. The mean night-time blood pressure were 8 and 7 mm Hg less than the day-time blood pressure for SBP and DBP, respectively.

Hypertensive patients recruited into this study had high BP both in the office and in their daily life. The average 24-hour BP value was lower than that of the office BP. This was essentially due to the large reduction in BP during the night.

Table 10: Office BP at the screening visit, office BP, 24-hour ABP and BP loads after placebo run-in period or at baseline (n=25)

	Office BP* at screening (mm Hg)	Office BP* (mm Hg)	24-hour ABP*					
			Average BP (mm Hg)			BP loads**		
						24-hour BP	Day-time BP	Night-time BP
			24-hour BP	Day-time BP	Night-time BP	Frequency[a] (%)	Frequency[a] (%)	Frequency[a] (%)
SBP	144 ± 9.39	154 ± 14.00	141 ± 12.09	143 ± 12.51	135 ± 12.59	51 ± 22.81	56 ± 23.91	79 ± 26.66
mild	143 ± 8.31	145 ± 8.36	140 ± 8.99	143 ± 8.60	131 ± 11.34	46 ± 19.31	57 ± 20.02	76 ± 24.38
moderate	144 ± 10.44	161 ± 13.32	142 ± 14.35	143 ± 15.24	138 ± 13.02	54 ± 25.35	55 ± 27.31	82 ± 28.95
DBP	86 ± 6.53	95 ± 9.29	92 ± 11.55	93 ± 12.46	86 ± 14.15	48 ± 34.07	48 ± 32.12	58 ± 34.82
mild	87 ± 7.64	89 ± 5.06	90 ± 10.19	92 ± 13.08	81 ± 12.79	46 ± 36.40	44 ± 31.91	46 ± 33.75
moderate	85 ± 5.60	100 ± 9.10	93 ± 12.71	93 ± 12.40	89 ± 14.72	49 ± 33.44	51 ± 33.16	69 ± 33.30
MAP	105 ± 5.41	115 ± 8.42	108 ± 10.34	110 ± 11.36	102 ± 11.59			
mild	106 ± 6.71	107 ± 4.66	107 ± 7.93	109 ± 9.97	98 ± 9.60			
moderate	105 ± 4.34	120 ± 5.98	109 ± 12.06	110 ± 12.70	105 ± 12.31			
HR (bpm)	74 ± 8.19	78 ± 9.11	78 ± 9.48	81 ± 9.51	67 ± 10.62			
mild	75 ± 11.22	75 ± 9.95	79 ± 8.57	82 ± 8.20	69 ± 10.15			
moderate	74 ± 5.11	80 ± 8.24	77 ± 10.40	80 ± 10.65	65 ± 11.06			

* data are shown as mean ± SD

** BP loads were BP values that higher than 140 or 120 mm Hg for SBP and 90 or 80 mm Hg for DBP during day-time and night-time, respectively

[a] frequency of BP loads is the percentage of BP loads

SBP = systolic blood pressure, DBP= diastolic blood pressure, MAP = mean arterial pressure [=DBP+1/3 (difference between SBP and DBP)], HR= heart rate respectively

24-hour ABP= average BP during 24 hours, day-time BP= average BP during 06.00 a.m.-09.00 p.m., night-time = average BP during 09.00 p.m.-06.00 a.m. by ambulatory blood pressure monitoring machine

By using the 24-hour BP monitoring, blood pressure variability throughout the day could be observed. It was found that BP was maintained at high level during awakening especially in the early morning, this is called the " morning surge " and was reduced to a lower level during sleeping time. This early morning rise in BP could contribute to the occurrence of cardiovascular events, such as acute myocardial infarction, sudden cardiac death, stable angina pectoris in the early morning hours. Furthermore, these events also had been assumed to be associated with the rapid morning increase in sympathetic activity, peripheral resistance leading to an increased myocardial oxygen consumption, together with an increased in thrombotic events and a decrease in fibrinolytic activity at that time[15,17]. In both normotensive and hypertensive individuals, BP varies according to both mental and physical activity levels which are usually different during wakefulness and during sleep. As shown in Figure 6, it was found that BP was at their highest levels during the period when the patients was awaked and active (06.00 a.m. to 07.00 p m.) and at their lowest levels during the sleeping period (08.00 p.m. to 05.00 a.m.)

With the categorization of hypertensive patients as dippers and non-dippers according to the percentage of BP decline of night-time BP compared to day-time BP. In this study as shown in Table 11, the percentage of BP nocturnal of night-time compared to day-time were 5.31 ± 6.74, 7.54 ± 10.25, and 6.66 ±7.19 %, by SBP, DBP, and MAP, respectively. However, some studies found that the reliability of SBP dipping was somewhat lower than that of diastolic or mean arterial blood pressure (MAP) dipping[70]. In addition, this study was mainly categorized the hypertensive patients by MAP nocturnal decline. With this criterion, nineteen patients (76%) were non-dippers while six patients (24%) were dippers.

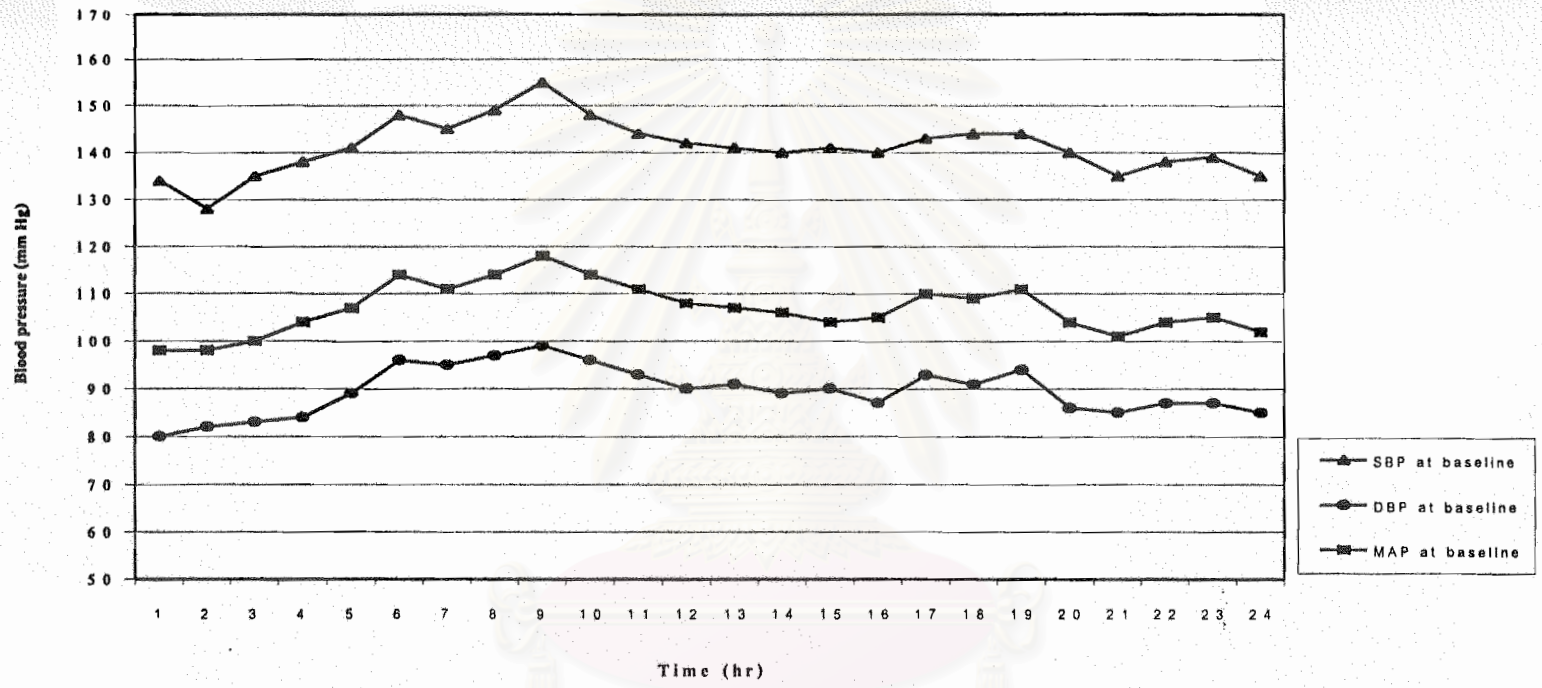

Figure 6: Ambulatory Hourly Blood Pressure Data of subjects at baseline (n=25)

Table 11: Percentage of nocturnal decline in blood pressure and number (percentage) of subjects who were dippers when classified by SBP, DBP and MAP at baseline (n=25)

	Percentage of nocturnal decline			Number (percentage) of dippers											
				SBP				DBP				MAP			
	SBP*	DBP*	MAP*	ID	ND	D	ED	ID	ND	D	ED	ID	ND	D	ED
	5.31 ± 6.74 (-9.2 – 16.8)	7.54 ± 10.25 (-7.1 – 42.6)	6.66 ± 7.19 (-1.9 – 30.0)	4 (16)	13 (52)	8 (32)	0 (0)	5 (20)	12 (48)	7 (28)	1 (4)	4 (16)	15 (60)	5 (20)	1 (4)
mild	8.28 ± 5.25 (-1.3 – 16.8)	10.85 ± 11.99 (-2.4 – 42.6)	9.85 ± 7.91 (-1.9 – 30.0)	1 (4)	6 (24)	4 (16)	0 (0)	1 (4)	6 (24)	3 (12)	1 (4)	1 (4)	7 (28)	2 (8)	1 (4)
moderate	2.97 ± 7.02 (-9.2 – 13.1)	4.94 ± 8.18 (-7.1 – 18.1)	4.15 ± 5.64 (-1.6 – 14.4)	3 (12)	7 (28)	4 (16)	0 (0)	4 (16)	6 (24)	4 (16)	0 (0)	3 (12)	8 (32)	3 (12)	0 (0)

* data are shown as mean ± SD

ID = inverted dipper (nocturnal decline less than 0%)

ND = non dipper (nocturnal decline 0% - less than 10%)

D = dipper (nocturnal decline 10% - less than 20%)

ED = extreme dipper (nocturnal decline 20% or more)

The non-dippers or flat pattern of circadian BP variability is clinically important since recent studies suggest that these patients appear to have an increase in cardiovascular morbidity. In addition, there is some evidence that non-dippers have a greater left ventricular mass than dippers[13,15,17,23].

Furthermore, with the observation of BP measured throughout the day, the SBP/DBP values that were higher than 140/90 mm Hg during day-time and 120/80 mm Hg during night-time were judged as anomalous value or elevated values or BP loads. BP loads were the percentage of systolic/diastolic values exceeding the aforementioned median values during the awake and the asleep periods for the entire 24-hour of blood pressure reading. BP loads were related to left ventricular mass index (LVMI) and left atrial index more strongly than were the mean 24-hour blood pressure values[69]. The frequency of BP loads were also shown in Table 10. It was found that the hypertensive patients possed high percentage of BP loads which was presented both during day-time and night-time. When 24-hour BP was evaluated, the percentage of elevated BP values higher than 140/90 mm Hg were 51 ± 22.8 / 48 ± 34.07 % while 56 ± 23.91 % of SBP and 48 ± 32.12 % of DBP obtained during day-time were anomalous. During night-time, percentage of anomalous values (SBP/DBP) which was higher than 120/80 mm Hg were 79 ± 26.66 / 58 ± 34.82 %. From this study, it was found that night-time BP loads were higher than day-time BP loads.

3. 24-hour urine collection data of the patients at baseline

24-hour urine collection data of the patients in this study at baseline were summarized in Table 12 and were demonstrated in Appendix E. 24-hour urinary excretion was obtained for determination of sodium and calcium excretion. Baseline urinary sodium and calcium was determined, when the patients were consuming their customary. The data of twenty-one patients only were used to calculated in the study since four patients had their total creatinine in the 24-hour urine specimen fell below the normal range, which mean that the collection might be incomplete. Almost all of these patients had normal levels of 24-hour urine collection data. Three patients who showed high urinary sodium excretion (>220 mEq/24hr) were associated with high blood pressure, all of them were classified as moderate hypertension. From INTERSALT study, it was found that there was a significant, positive independent linear relation between 24-hour sodium excretion and SBP/DBP[45]. While one patient who showed high urinary calcium excretion (>250 mg/24hr) was classified as moderate hypertension. These results were consistent with a previous study which indicated that hypertensive individuals excreted more calcium both under basal circumstance and during a calcium infusion than normotensive subjects[59].

Creatinine clearance (Clcr) is a specific measurement of renal function that requires a 24-hour urine collection. It more accurately reflects renal function than the serum creatinine. But urine collection are time-consuming and expensive. As a result, several nomograms and formulas have been developed to provide estimates of creatinine clearance by using measured serum creatinine values[71]. In this study, Cockcroft and Gault formula was used to

Table 12: 24- hour urine collection data of the mild and moderate hypertensive subjects at baseline (n=21)

Test (normal range)[a]	Mean ±SD	Range
Creatinine (1000-2000 mg/24hr)	1053.38 ± 326.72	459.00 – 1876.00
mild	1059.22 ± 256.15	680.00 – 1518.00
moderate	1048.99 ± 382.51	459.00 – 1876.00
Sodium (40-220 mEq/24hr)	156.28 ± 78.72	77.90 – 430.90
mild	145.56 ± 36.65	82.00 – 213.90
moderate	164.32 ± 100.62	77.90 – 430.90
Calcium (50-250 mg/24hr)	136.49 ± 79.94	10.80 – 349.20
mild	123.44 ± 59.98	50.60 – 237.60
moderate	146.28 ± 93.59	10.80 – 349.20
% FENa	0.98 ± 0.39	0.44 – 2.42
mild	0.91 ± 0.19	0.67 – 1.31
moderate	1.04 ± 0.49	0.44 – 2.42
% FECal	1.23 ± 0.61	0.22 – 2.91
mild	1.11 ± 0.44	0.43 – 1.66
moderate	1.32 ± 0.72	0.22 – 2.91
Clcr (from laboratory) (ml/min)	78.58 ± 20.17	35.42 – 120.83
mild	79.17 ± 14.00	61.96 – 112.50
moderate	78.13 ± 24.43	35.42 – 120.83
Clcr (calculated) (ml/min)	62.27 ± 17.97	24.15 – 96.28
mild	64.42 ± 14.11	46.40 – 93.20
moderate	60.67 ± 20.88	24.15 – 96.28

FENa, fractional excretion of sodium; FECal, fractional excretion of calcium

$$\%\,FENa = \frac{U_{Na} * Scr * 100}{S_{Na} * Ucr}, \quad \%\,FECal = \frac{U_{cal} * Scr * 100}{S_{cal} * Ucr}$$

$$Clcr\ (from\ laboratory) = \frac{Ucr\ (mg/dl) * Volume\ (ml)}{Scr\ (mg/dl) * 1440},$$

$$Clcr\ (calculated) = \frac{(140\text{-}age) * IBW}{72 * Scr}\ (*0.85\ for\ female)$$

[a] = normal range at King Chulalongkorn Memorial Hospital

estimate the creatinine clearance of the patients from their serum creatinine values because this formula has the highest correlation and the greatest accuracy in patients with serum creatinine concentrations <1.5mg/dl[71]. Most Clcr values calculated by using 24-hour urine collection were higher than those obtained from using Cockcroft and Gault formula, with the exception of two patients whose Clcr calculated by using 24-hour urine collection were lower than those obtained from using the formula. These two patients had their total creatinine in the 24-hour urine specimen fell below the normal range. Majority of these patients had normal levels of laboratory data indicated that the patients in this study had normal renal function.

4. Antihypertensive effect evaluation

4.1 Therapeutic effects of HCTZ and $CaCO_3$ on blood pressure

Office Blood pressure

After patients in group 1 had received treatment with hydrochlorothiazide 25 mg per day in combination with placebo of calcium carbonate ($CaCO_3$) 1 gm twice daily for 4 weeks, it was found that office SBP and DBP were significantly decreased, passing from 161 $\pm$ 13.07 / 95 $\pm$ 9.14 mm Hg to 144 $\pm$ 11.24 / 84 $\pm$ 7.34 mm Hg ($p<0.01$). After $CaCO_3$ 1 gm twice daily had been used in place of placebo for another 4 weeks, the office SBP/DBP were decreased to 142 $\pm$ 13.00 / 85 $\pm$ 9.94 mm Hg. These BP were significantly different from the pre-treated values at $p<0.001$, $p<0.01$, respectively. MAP were also significantly lowered from 117 $\pm$ 7.13 to 104 $\pm$ 7.99 mm Hg ($p<0.001$) after the first 4 weeks when hydrochlorothiazide was used alone and to 104 $\pm$ 10.22 mm Hg after hydrochlorothiazide was used in combination with $CaCO_3$ for another 4 weeks ($p<0.001$). However, there were no significant changes in HR after either

regimen. The HR were recorded to be 78 ± 11.34 bpm before treatment 78 ± 11.69 bpm after the first 4 weeks treatment (p=0.05-0.10) and 76 ± 7.33 bpm after the second 4 weeks treatment (p=0.21-0.30) (Table 13).

In contrary, for patients in group 2, their office SBP was negligible decreased (p>0.31) and office DBP, MAP, and HR were slightly reduced between baseline and after either treatment, whether the treatment was $CaCO_3$ 1 gm twice daily combined with placebo of HCTZ for one month or $CaCO_3$ 1 gm twice daily in combination with HCTZ 25 mg OD for another 4 weeks (p=0.05-0.10). There were also no significant differences in the reduction of SBP, DBP and MAP between the first 4 weeks and the second 4 weeks treatments (p>0.31) (Table 14, Figure 7-9).

Ambulatory Blood pressure

Average 24-hour BP

By 24-hour BP evaluation, SBP and DBP were significantly reduced from 143 ± 9.83 / 93 ± 14.83 to 133 ± 14.20 / 80 ± 14.49 mm Hg with HCTZ 25 mg OD treatment for 4 weeks (group 1) (p<0.05) and to 133 ± 12.19 / 80 ± 7.63 mm Hg after combined with $CaCO_3$ 1 gm twice daily for another 4 weeks (p<0.01). MAP was also significantly lowered from 110 ± 11.92 to 97 ± 13.42 mm Hg after HCTZ alone treatment and to 97 ± 7.78 mm Hg after combination treatment (p<0.01). Only small further reduction in SBP, DBP, and MAP were obtained after CaCO3 was added on HCTZ for therapy (p>0.31) (Table 14, Figure 10-12). HR was significantly decreased from 79 ± 11.01 bpm before treatment to 75 ± 10.84 bpm and 76 ± 8.42 bpm (p<0.05) after the first 4 weeks and the second 4 weeks, respectively.

Table 13: Office BP and 24-hour ABP of the subjects at baseline and after treatment with hydrochlorothiazide or $CaCO_3$ alone and when used the two drugs in combination

Parameter	Baseline (n=25)	HCTZ + $CaCO_3$ (n=25) [a]	Group 1 (n=12)			Group 2 (n=13)		
			Baseline	HCTZ [a]	HCTZ + $CaCO_3$ [a,b]	Baseline	$CaCO_3$ [a]	$CaCO_3$ + HCTZ [a,b]
Office BP (mean ± SD)								
SBP (mm Hg)	154 ± 14.00	142 ± 18.36**	161 ± 13.07	144 ± 11.24***	142 ± 13.00$^{***,+}$	148 ± 12.02	147 ± 15.66^{+}	142 ± 22.80$^{++,+}$
DBP (mm Hg)	95 ± 9.29	89 ± 9.59**	95 ± 9.14	84 ± 7.34**	85 ± 9.94$^{**,+}$	95 ± 9.81	93 ± 8.90^{++++}	92 ± 8.08$^{++,+}$
MAP (mm Hg)	115 ± 8.42	107 ± 11.16***	117 ± 7.13	104 ± 7.99***	104 ± 10.22$^{***,+}$	113 ± 9.28	111 ± 10.38^{++++}	109 ± 11.86$^{++++,+}$
HR (bpm)	78 ± 9.11	77 ± 8.10^{+}	78 ± 11.34	78 ± 11.69^{+}	76 ± 7.33$^{++,+}$	77 ± 6.90	75 ± 7.31^{++}	79 ± 8.74$^{+,+++}$
24 – hour ABP (mean ± SD)								
-average 24-hour								
SBP (mm Hg)	141 ± 12.09	134 ± 14.69*	143 ± 9.83	133 ± 14.20*	133 ± 12.19$^{**,+}$	139 ± 13.92	138 ± 14.89^{+}	134 ± 17.16$^{+,+}$
DBP (mm Hg)	92 ± 11.55	81 ± 9.65***	93 ± 14.83	80 ± 14.49*	80 ± 7.63$^{**,+}$	90 ± 7.83	85 ± 11.61^{++++}	83 ± 11.30$^{*,+}$
MAP (mm Hg)	108 ± 10.34	99 ± 10.35***	110 ± 11.92	97 ± 13.42**	97 ± 7.78$^{**,+}$	107 ± 8.84	103 ± 12.06^{++}	100 ± 12.47$^{++++,+}$
HR (bpm)	78 ± 9.48	77 ± 7.01^{+}	79 ± 11.01	75 ± 10.84*	76 ± 8.42$^{*,+}$	76 ± 7.99	76 ± 9.54^{+}	77 ± 5.73$^{+,+}$
- average day-time								
SBP (mm Hg)	143 ± 12.51	136 ± 15.34*	145 ± 9.92	135 ± 12.12**	135 ± 12.19$^{**,+}$	141 ± 14.63	141 ± 13.82^{+}	137 ± 18.26$^{+,+}$
DBP (mm Hg)	93 ± 12.46	84 ± 9.72**	94 ± 13.18	82 ± 14.60*	82 ± 7.52$^{*,+}$	91 ± 12.09	87 ± 9.98^{+++}	84 ± 11.66$^{++++,+}$
MAP (mm Hg)	110 ± 11.36	101 ± 10.56**	112 ± 11.28	100 ± 12.15**	100 ± 7.58$^{**,+}$	108 ± 11.58	105 ± 10.70^{+}	102 ± 12.99$^{++++,+}$
HR (bpm)	81 ± 9.51	78 ± 6.94^{++}	82 ± 11.77	77 ± 11.99*	79 ± 8.95$^{++++,+}$	80 ± 7.21	80 ± 10.49^{+}	80 ± 4.74$^{+,+}$
- average night-time								
SBP (mm Hg)	135 ± 12.59	127 ± 15.49**	138 ± 11.87	127 ± 18.96*	127 ± 15.26$^{**,+}$	132 ± 13.01	133 ± 16.87^{+}	127 ± 16.31$^{++,+++}$
DBP (mm Hg)	86 ± 14.15	74 ± 10.33***	89 ± 17.88	75 ± 14.86*	71 ± 10.32$^{**,++}$	83 ± 9.34	81 ± 15.52^{+}	76 ± 10.13$^{**,+++}$
MAP (mm Hg)	102 ± 11.59	92 ± 10.52***	106 ± 14.02	93 ± 15.51*	90 ± 9.50$^{***,+}$	99 ± 8.33	98 ± 14.81^{+}	93 ± 11.55$^{*,++++}$
HR (bpm)	67 ± 10.62	68 ± 10.78^{+}	68 ± 10.46	68 ± 11.12^{+}	69 ± 11.98$^{+,+}$	66 ± 11.03	67 ± 9.10^{+}	68 ± 10.02$^{+,+}$

a compared to baseline of each group, b compared to before combination of the second drug

*** p<0.001, ** p<0.01, *p<0.05, ++++ p=0.05-0.10, +++ p=0.11-0.20, ++ p=0.21-0.30, + p>0.31

Table 14: Comparison of office BP and 24- hour ABP after treatment with hydrochlorothiazide or $CaCO_3$ alone as compared to baseline and after combination of the two drugs as compared to one drug

Parameter	Comparison of office BP and 24- hour ABP (mm Hg)					
	Group 1 (n=12)			Group 2 (n=13)		
	HCTZ vs baseline[a] (1)	HCTZ + $CaCO_3$ vs baseline[a] (2)	(2) – (1)[b]	$CaCO_3$ vs baseline[a] (3)	$CaCO_3$ + HCTZ vs baseline[a] (4)	(4) – (3)[b]
Office BP						
SBP (mm Hg)	$\downarrow 17^{***}$	$\downarrow 19^{***}$	$\downarrow 2^{+}$	$\downarrow 1^{+}$	$\downarrow 6^{++}$	$\downarrow 5^{+}$
DBP (mm Hg)	$\downarrow 11^{**}$	$\downarrow 10^{**}$	$\uparrow 1^{+}$	$\downarrow 2^{++++}$	$\downarrow 3^{++}$	$\downarrow 1^{+}$
MAP (mm Hg)	$\downarrow 13^{***}$	$\downarrow 13^{***}$	$\downarrow 0.2^{+}$	$\downarrow 2^{++++}$	$\downarrow 4^{++++}$	$\downarrow 2^{+}$
24 – hour ABP						
- average 24-hour						
SBP (mm Hg)	$\downarrow 10^{*}$	$\downarrow 10^{**}$	$\downarrow 0.3^{+}$	$\downarrow 1^{+}$	$\downarrow 5^{+}$	$\downarrow 4^{+}$
DBP (mm Hg)	$\downarrow 13^{*}$	$\downarrow 13^{**}$	$\downarrow 0.2^{+}$	$\downarrow 5^{++++}$	$\downarrow 7^{*}$	$\downarrow 2^{+}$
MAP (mm Hg)	$\downarrow 13^{**}$	$\downarrow 13^{**}$	$\downarrow 0.1^{+}$	$\downarrow 4^{++}$	$\downarrow 7^{++++}$	$\downarrow 3^{+}$
- average day-time						
SBP (mm Hg)	$\downarrow 10^{**}$	$\downarrow 10^{**}$	$\uparrow 0.4^{+}$	$\downarrow 0.3^{+}$	$\downarrow 4^{+}$	$\downarrow 4^{+}$
DBP (mm Hg)	$\downarrow 12^{*}$	$\downarrow 12^{*}$	$\uparrow 0.5^{+}$	$\downarrow 4^{+++}$	$\downarrow 7^{++++}$	$\downarrow 3^{+}$
MAP (mm Hg)	$\downarrow 12^{**}$	$\downarrow 12^{**}$	$\uparrow 0.5^{+}$	$\downarrow 3^{+}$	$\downarrow 6^{++++}$	$\downarrow 3^{+}$
- average night-time						
SBP (mm Hg)	$\downarrow 11^{*}$	$\downarrow 11^{**}$	$\uparrow 0.6^{+}$	$\uparrow 1^{+}$	$\downarrow 5^{++}$	$\downarrow 6^{+++}$
DBP (mm Hg)	$\downarrow 14^{*}$	$\downarrow 18^{**}$	$\downarrow 4^{++}$	$\downarrow 2^{+}$	$\downarrow 7^{**}$	$\downarrow 5^{+++}$
MAP (mm Hg)	$\downarrow 13^{*}$	$\downarrow 16^{***}$	$\downarrow 3^{+}$	$\downarrow 1^{+}$	$\downarrow 6^{*}$	$\downarrow 5^{++++}$

a compared to baseline of each group, b compared to before combination of the second drug

*** p<0.001, ** p<0.01, *p<0.05, ++++ p=0.05-0.10, +++ p=0.11-0.20, ++ p=0.21-0.30, + p>0.31

In controversy, patients (group 2) who started their treatment by received $CaCO_3$ 1 gm twice daily plus placebo of HCTZ were found to have their SBP, DBP, MAP and HR reduced from 139 ± 13.92, 90 ± 7.83, 107 ± 8.84 mm Hg, and 76± 7.99 bpm to 138 ± 14.89, 85 ± 11.61, 103 ± 12.06 mm Hg, and 76 ± 9.54 bpm, respectively ($p>0.05$). These reductions were so small that they were not statistically significant. After HCTZ 25 mg OD was added on as a combination therapy for another 4 weeks, SBP was reduced to 134 ± 17.16 mm Hg ($p>0.31$) while DBP was significantly reduced to 83 ± 11.30 mm Hg ($p<0.05$). MAP was decreased to 100 ± 12.47 mm Hg ($p=0.05$-0.10). Only small further reduction in SBP, DBP, and MAP were found after HCTZ was added on the therapy, which were not statistically significant ($p>0.31$) (Table 14, Figure 10-12).

Average day-time BP

When the BP during day-time hours only were considered, it was found that the mean day-time SBP and DBP were significantly dropped from baseline values of 145 ± 9.92 / 94 ± 13.18 mm Hg to 135 ± 12.12 / 82 ± 14.60 mm Hg after HCTZ 25 mg OD treatment for 4 weeks (group 1) and to 135 ± 12.19 / 82 ± 7.52 mm Hg after combined with $CaCO_3$ 1 gm twice daily for another 4 weeks (these differences were statistically significant at $p<0.01$ and $p<0.05$, respectively). MAP was also significantly lowered from baseline values of 112 ± 11.28 mm Hg to 100 ± 12.15 mm Hg ($p<0.01$) after HCTZ treatment and to 100 ± 7.58 mm Hg ($p<0.01$) after HCTZ plus $CaCO_3$ treatment. Only small further reduction in SBP, DBP, and MAP were observed after $CaCO_3$ had been combined ($p>0.31$) (Table 14, Figure 13-15). HR was significantly decreased from 82 ± 11.77 bpm before treatment to 77 ± 11.99 bpm after 4

weeks treatment with HCTZ ($p<0.05$) and was recorded to be 79 $\pm$ 8.95 bpm after HCTZ plus $CaCO_3$ treatment ($p=0.05$-0.10).

At the same time, patients (group 2) who started their regimen with $CaCO_3$ 1 gm twice daily first had been found to have their mean day-time SBP / DBP and MAP reduced from 141 $\pm$ 14.63 / 91 $\pm$ 12.09 mm Hg and 108 $\pm$ 11.58 mm Hg at baseline to 141 $\pm$ 13.82 / 87 $\pm$ 9.98 mm Hg and 105 $\pm$ 10.70 mm Hg, respectively ($p>0.05$). After HCTZ 25 mg OD had been combined for another 4 weeks, their SBP / DBP and MAP were recorded to be 137 $\pm$ 18.26 / 84 $\pm$ 11.66 mm Hg and 102 $\pm$ 12.99 mm Hg. Neither of these reductions in BP there were statistically significant at $p< 0.05$.

The further reductions in day-time hours SBP, DBP and MAP were not statistically significant differences in either group when compared the results of one drug treatment to two drugs combination treatment ($p>0.31$) (Table 14, Figure 13-15).

Average night-time BP

Patient (group1) who started their treatment with HCTZ 25 mg OD first for 4 weeks, the average night-time SBP / DBP, and MAP were significantly reduced from 138 $\pm$ 11.87 / 89 $\pm$ 17.88 mm Hg and 106 $\pm$ 14.02 mm Hg at baseline to 127 $\pm$ 18.96 / 75 $\pm$ 14.86 mm Hg and 93 $\pm$ 15.51 mm Hg, respectively ($p<0.05$). After $CaCO_3$ 1 gm BID had been combined, these BP had also been decreased from baseline to 127 $\pm$ 15.26 / 71 $\pm$ 10.32 mm Hg and 90 $\pm$ 9.50 mm Hg, respectively ($p<0.01$). However, only small extent of further reduction in SBP, DBP and MAP had been observed after the second drug had been added on and these were not statistically significant ($p>0.05$) (Table 14, Figure 16-18).

At the same time, patients (group 2) who took $CaCO_3$ 1 gm twice daily as their starting regimen showed their mean night-time SBP, DBP and MAP changed from 132 ± 13.01 / 83 ± 9.34 mm Hg and 99 ± 8.33 mm Hg at baseline to 133 ± 16.87 / 81 ± 15.52 mm Hg and 98 ± 14.81 mm Hg, respectively ($p>0.31$). After HCTZ 25 mg OD had been combined for 4 more weeks, their mean SBP was lowered from baseline to 127 ± 16.31 mm Hg ($p=0.21$-0.30) whereas DBP and MAP were significantly reduced from baseline to 76 ± 10.13 and 93 ± 11.55 mm Hg ($p<0.01$, $P<0.05$), respectively. The combination of the second drug showed only little further reduction in SBP, DBP, and MAP and were not statistically significant ($p>0.05$) (Table 14, Figure 16-18).

The results from this study showed that the antihypertensive effects of hydrochlorothiazide 25 mg per day was apparent not only from office blood pressure measurement, but also better reflected from the 24-hour ABP monitoring. This finding that hydrochlorothiazide 25 mg accounted for the reduction in office blood pressure of 17/11 mm Hg is similar to the results obtained from previous studies which suggested that HCTZ could lower SBP by 15 to 20 mm Hg and DBP by 8 to 15 mm Hg[1] and 24-hour MAP by was 7.8 mm Hg[50]. Calcium carbonate 1 gm twice daily, could reduced office BP by 1 / 2 mm Hg which is consistent with a previous study which found the effect of calcium supplement on blood pressure reduction were –0.89 mm Hg for SBP (95 %CI, -1.74 to –0.05 mm Hg) and –0.18 mm Hg for DBP (95% CI, -0.75 to 0.40 mm Hg)[53]. However, this study found that calcium supplement showed higher effect on DBP than SBP whether the measurements were recorded as office blood pressure, 24-ABP, day-time BP or night-time BP.

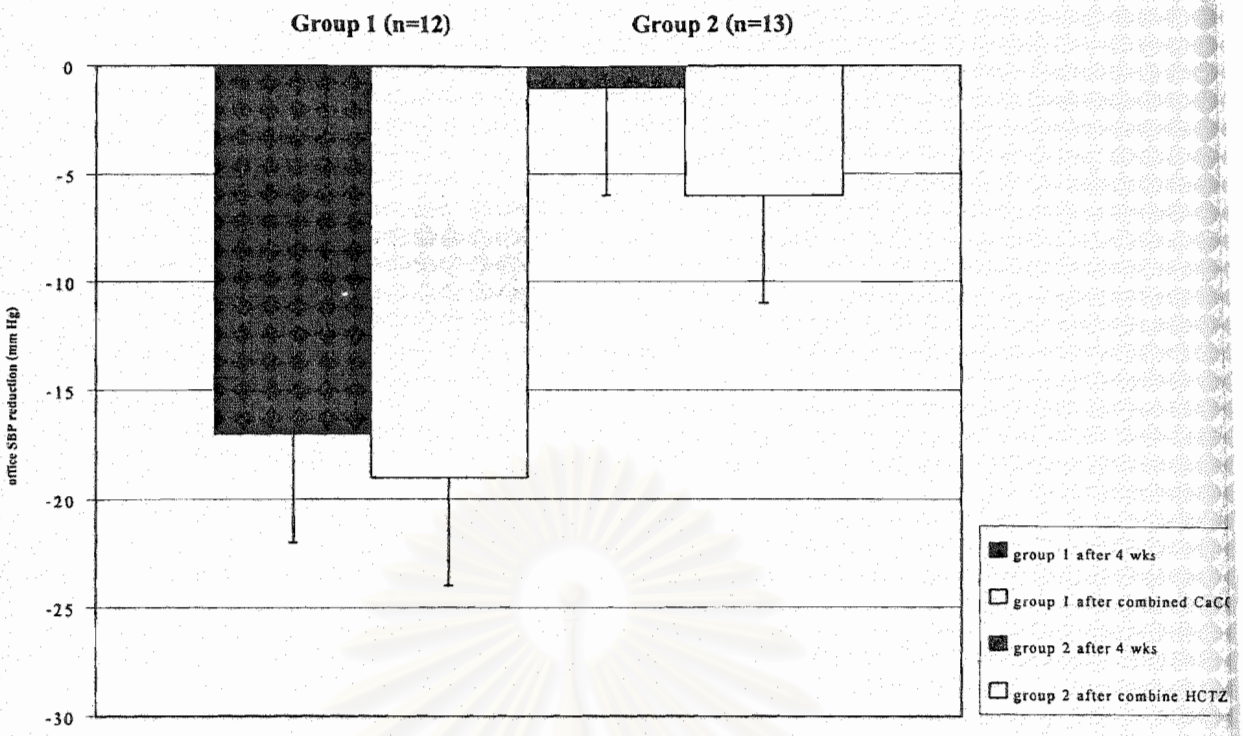

Figure 7: Office SBP reduction of group 1 (n=12) and group 2 (n=13) versus baseline

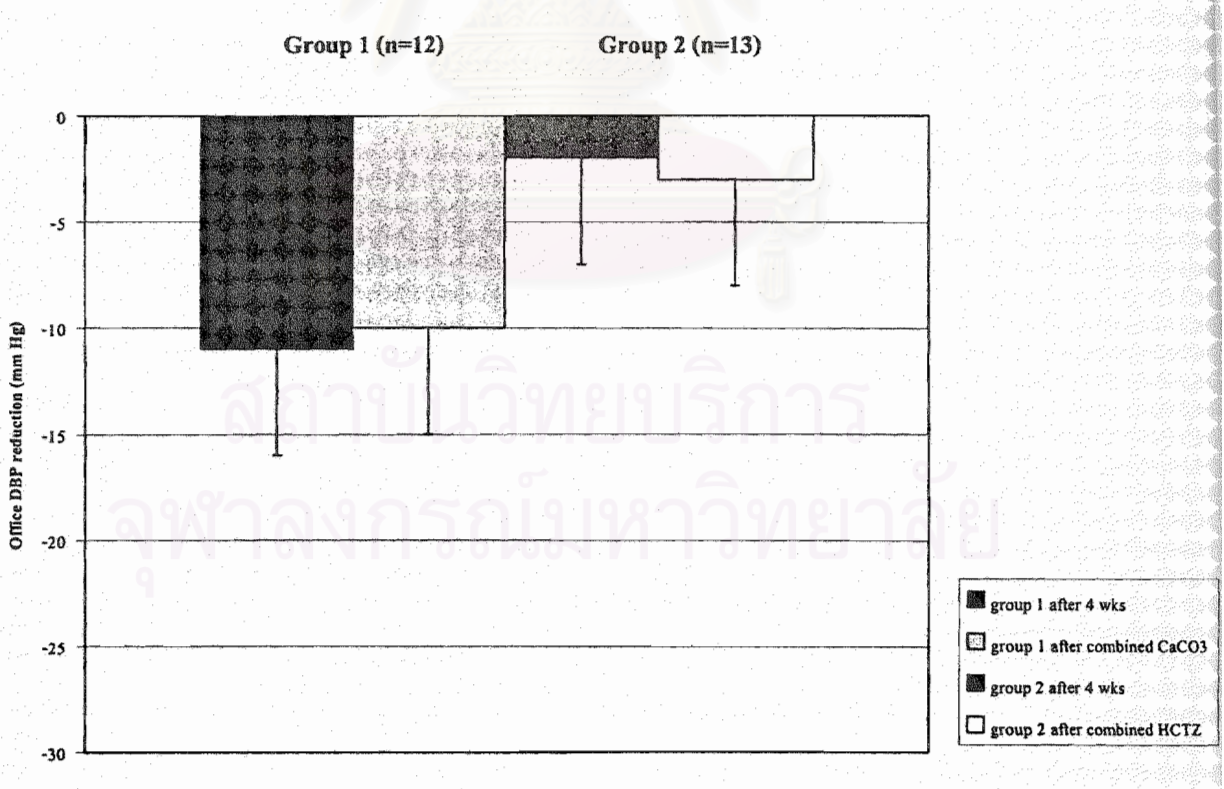

Figure 8: Office DBP reduction of group 1 (n=12) and group 2 (n=13) versus baseline

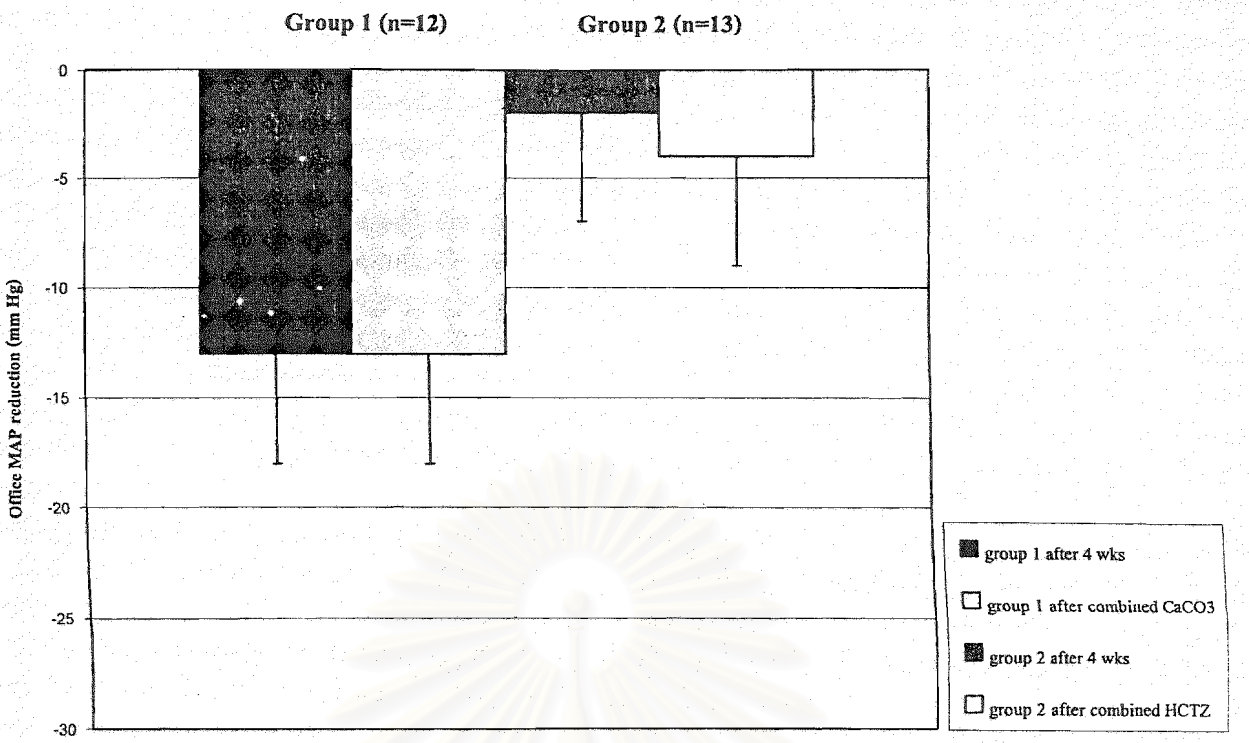

Figure 9: Office MAP reduction of group 1 (n=12) and group 2 (n=13) versus baseline

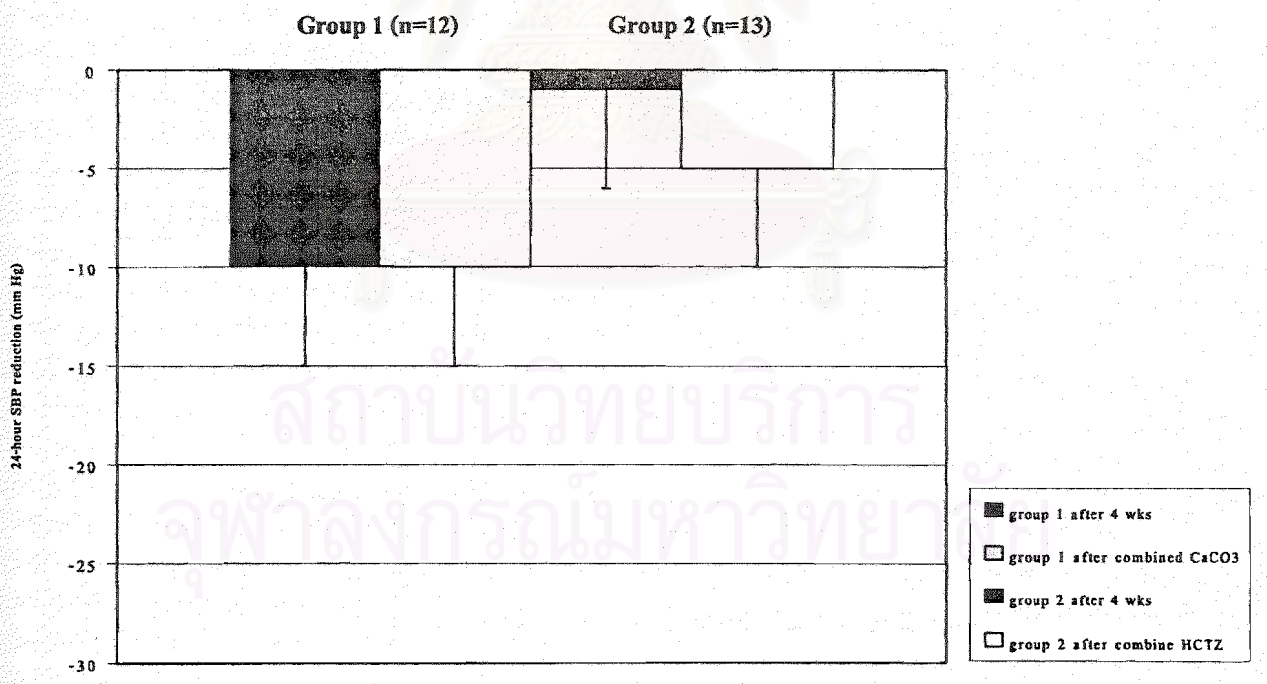

Figure 10: 24-hour SBP reduction of group 1 (n=12) and group 2 (n=13) versus baseline

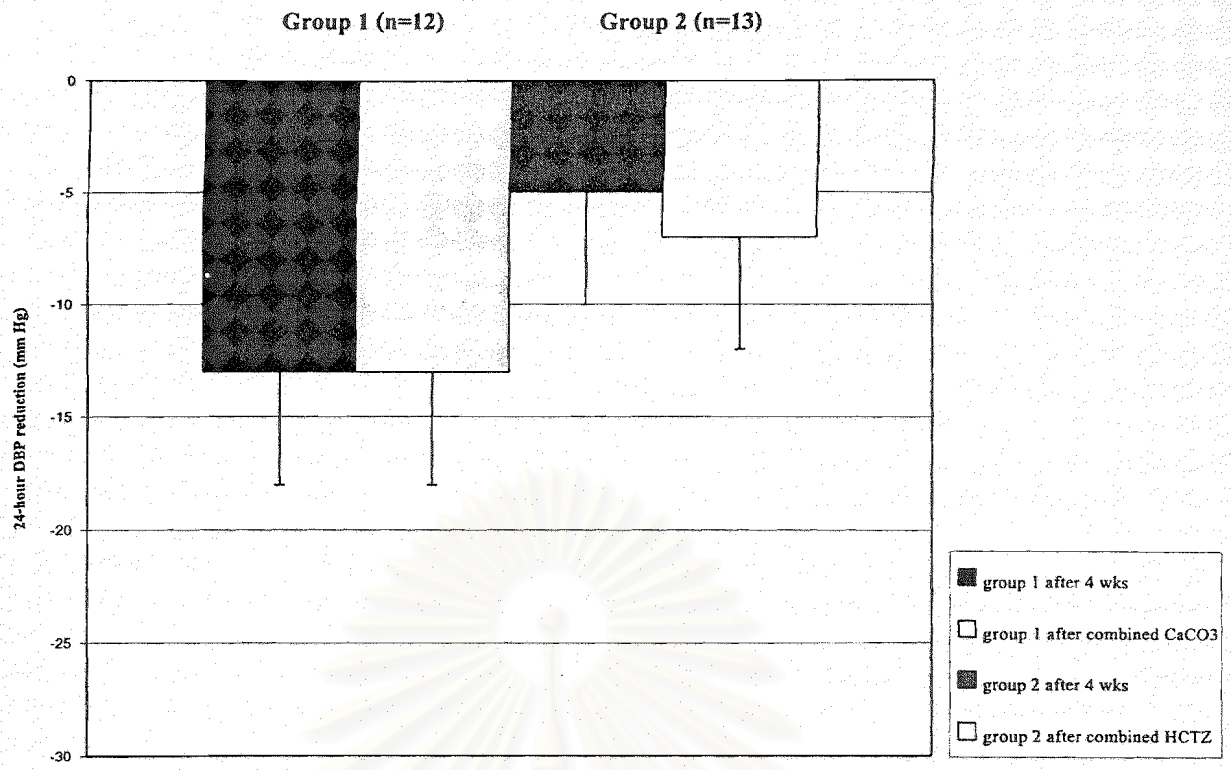

Figure 11: 24- hour DBP reduction of group 1 (n=12) and group 2 (n=13) versus baseline

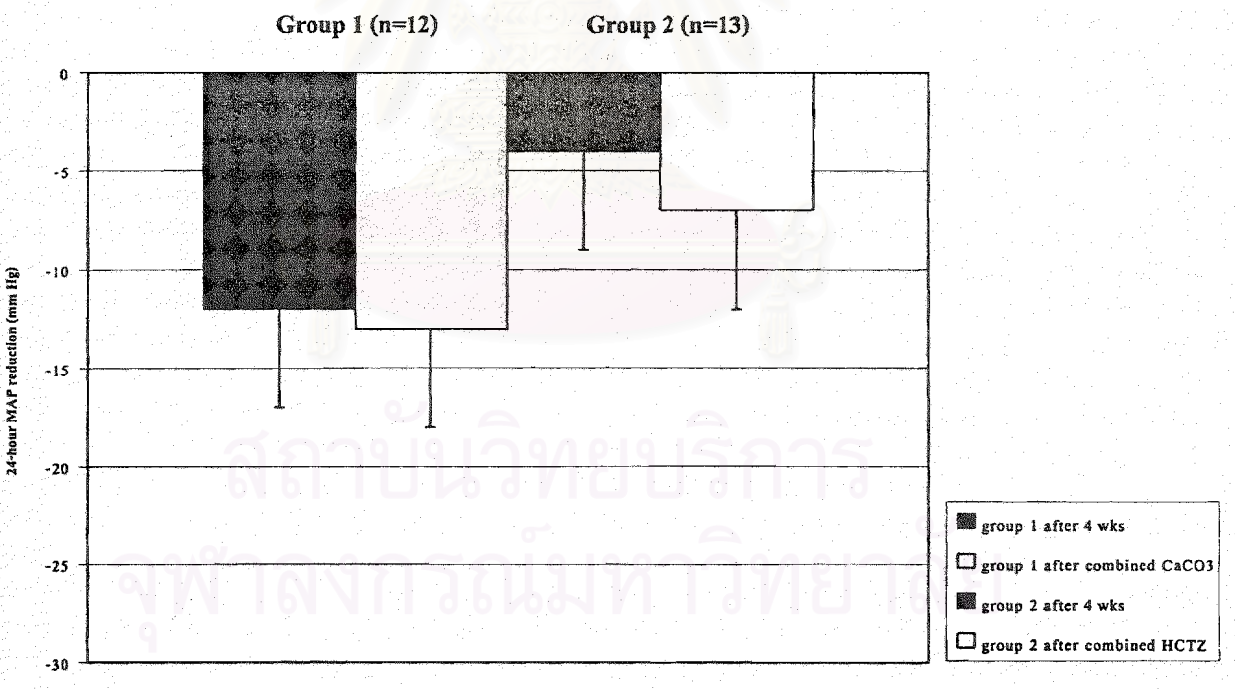

Figure 12: 24- hour MAP reduction of group 1 (n=12) and group 2 (n=13) versus baseline

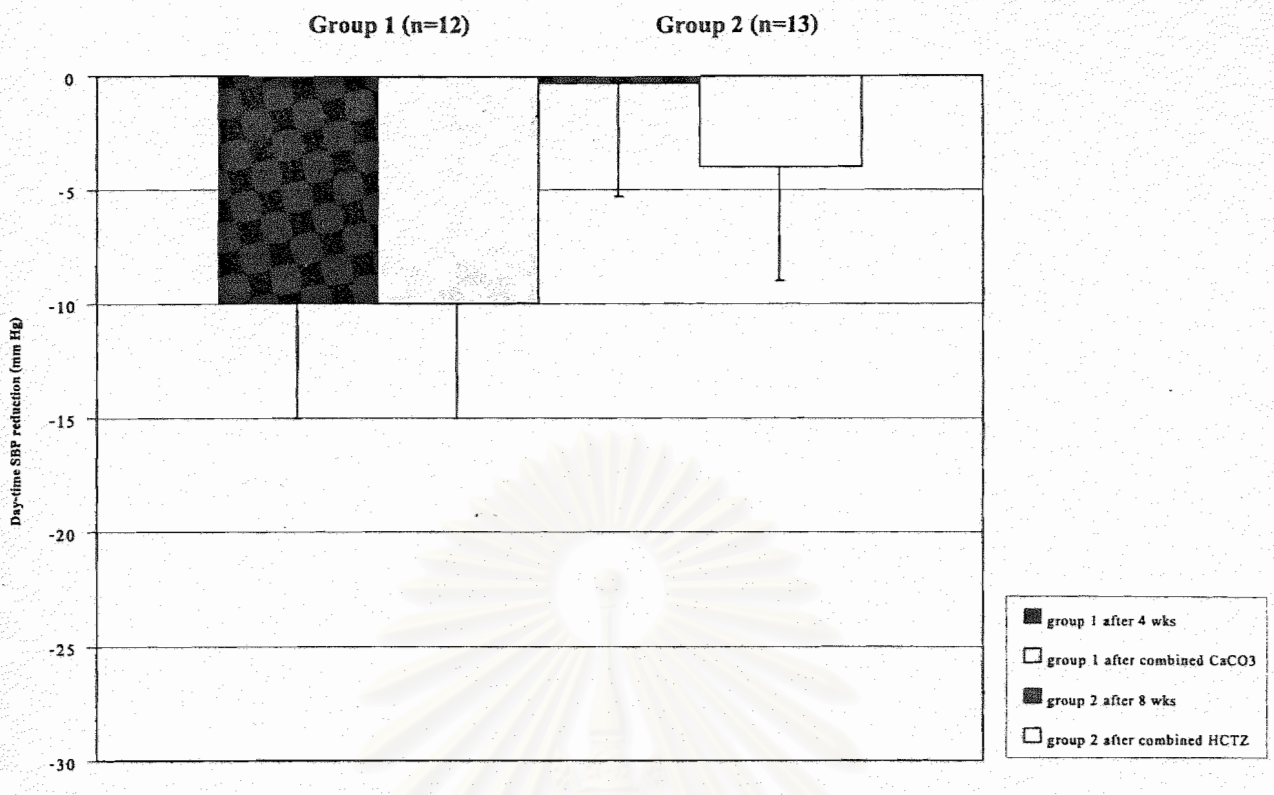

Figure 13: Day-time SBP reduction of group 1 (n=12) and group 2 (n=13) versus baseline

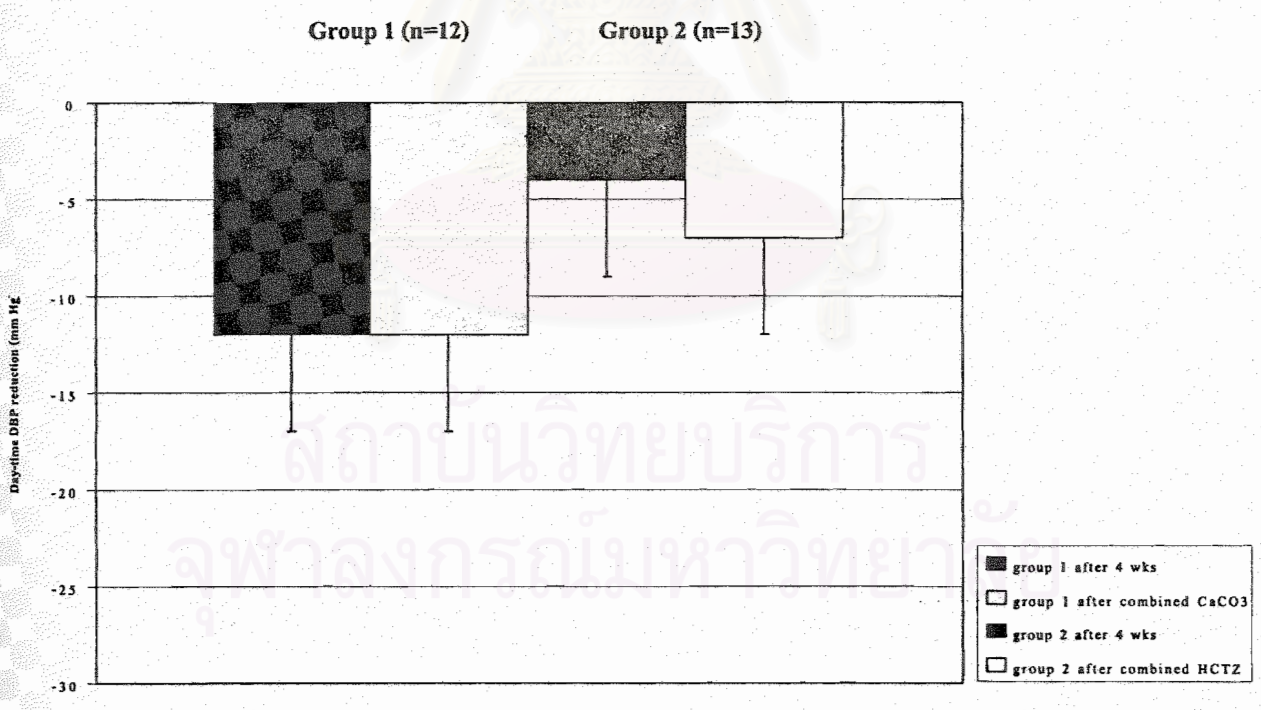

Figure 14: Day-time DBP reduction of group 1 (n=12) and group 2 (n=13) versus baseline

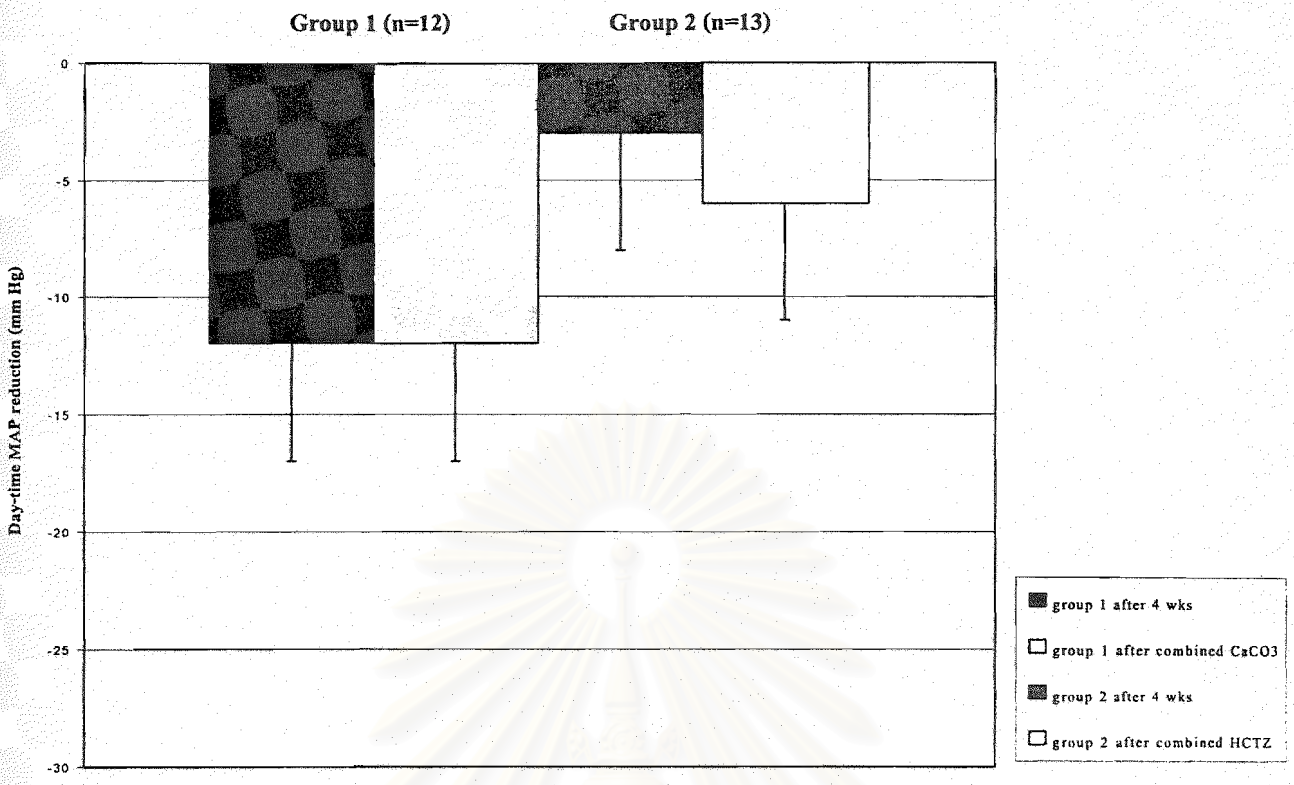

Figure 15: Day-time MAP reduction of group 1 (n=12) and group 2 (n=13) versus baseline

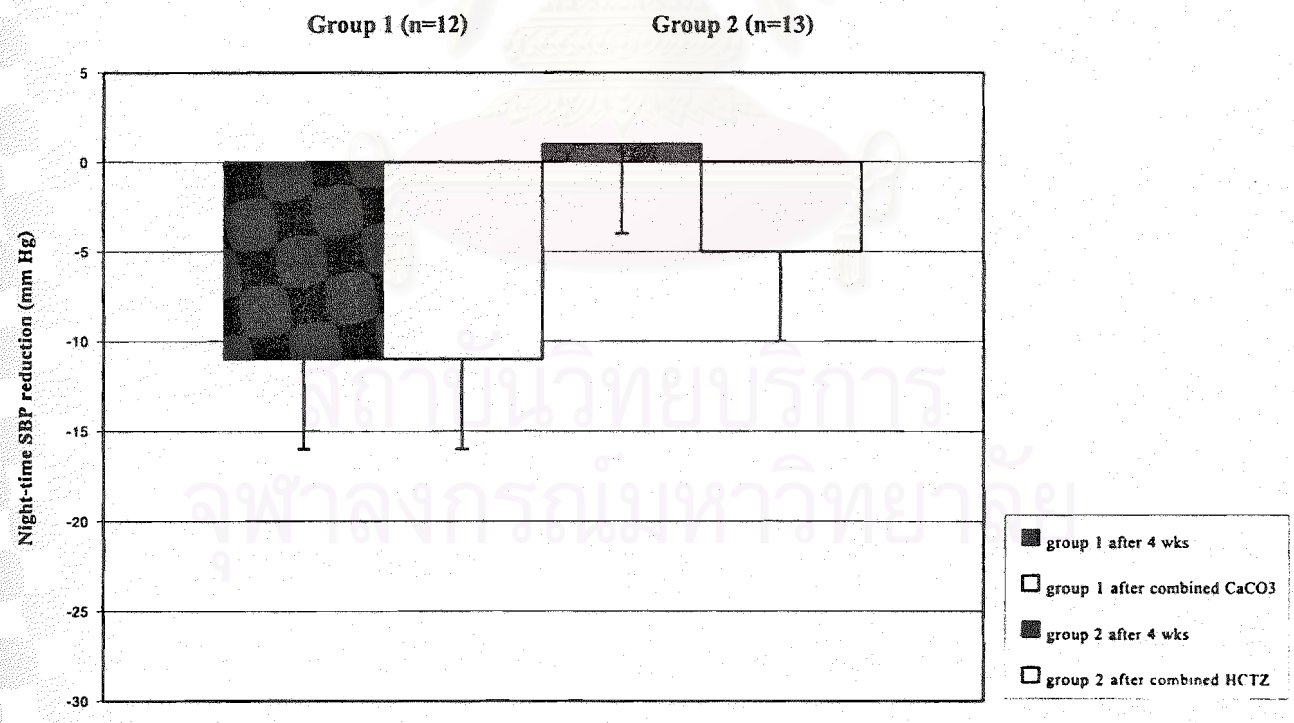

Figure 16: Night-time SBP reduction of group 1 (n=12) and group 2 (n=13) versus baseline

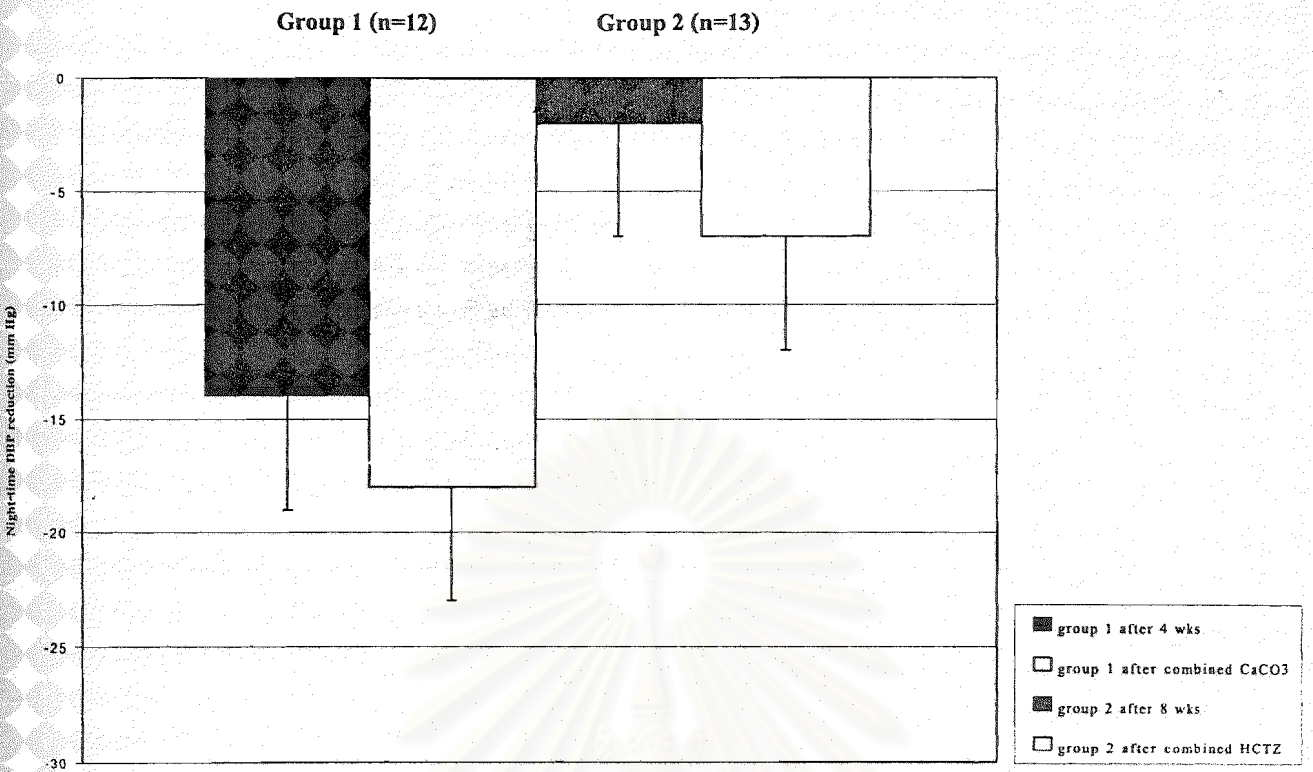

Figure 17: Night-time DBP reduction of group 1 (n=12) and group 2 (n=13) versus baseline

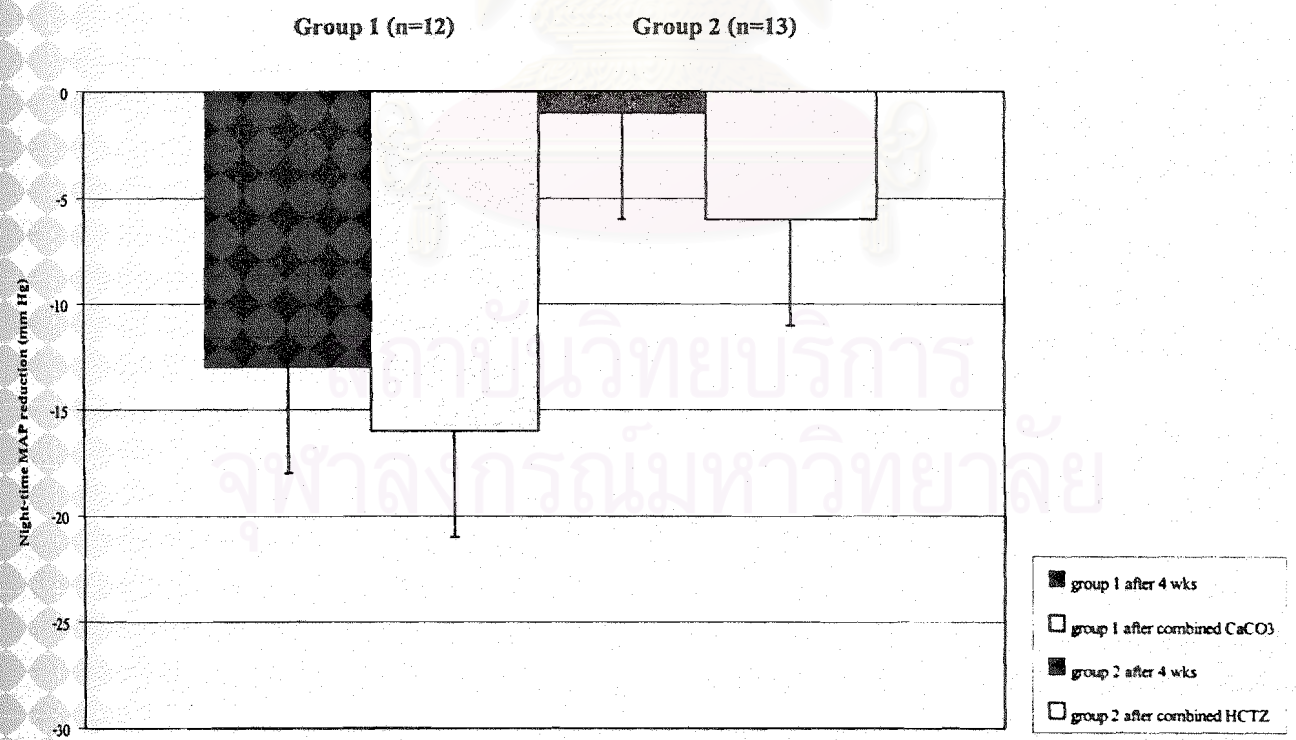

Figure 18: Night-time MAP reduction of group 1 (n=12) and group 2 (n=13) versus baseline

Patients were classified as mild and moderate hypertension based on their office SBP/DBP. Mild hypertensive patients were patients who had their office sitting SBP in the range of 140-159 mm Hg and/or DBP in the range of 90-99 mm Hg, if patients had office sitting SBP between 160-179 mm Hg and/or DBP between 100-109 mm Hg they were classified to be moderate hypertension. Patients (group 1) who started their treatment with HCTZ 25 mg OD first for 4 weeks, were found to have their office BP and 24-hour ambulatory BP decreased from baseline especially patients with moderate hypertension ($p<0.01$). After $CaCO_3$ 1 gm BID had been combined for another 4 weeks BP of mild hypertensive patients only were further reduced ($p=0.05$-0.10) (Table 15-17).

At the same time, mild hypertensive patients (group 2) who took $CaCO_3$ 1 gm twice daily as their starting regimen showed small decrease in their office and 24-hour ambulatory blood pressure from baseline but not in the levels which were considered as statistically significant ($p>0.05$). After HCTZ 25 mg OD was added on as a combination therapy for another 4 weeks, their mean office SBP and 24-hour ABP were significantly decreased from baseline ($p<0.01$). While moderate hypertensive patients after treatment with $CaCO_3$, their BP were not decreased but even higher than their baseline values. After HCTZ 25 mg OD had been combined for 4 more weeks, their mean office SBP and 24-hour ABP were reduced especially night-time higher than when $CaCO_3$ had been used alone ($p>0.31$).

Table 15: Office BP and 24-hour ABP of the subjects at baseline and after treatment with hydrochlorothiazide or $CaCO_3$ alone and when used the two drugs in combination

(mild hypertension based on office SBP/DBP at baseline)

Parameter	Baseline	HCTZ + $CaCO_3$	Group 1 (n=4)			Group 2 (n=7)		
	(n=11)	(n=11) [a]	Baseline	HCTZ [a]	HCTZ + $CaCO_3$ [a,b]	Baseline	$CaCO_3$ [a]	$CaCO_3$ + HCTZ [a,b]
Office BP (mean ± SD)								
SBP (mm Hg)	145 ± 8.36	129 ± 11.67**	151 ± 7.23	144 ± 7.81^{+++}	133 ± 16.03$^{++++,++++}$	142 ± 7.53	137 ± 8.40^{++++}	127 ± 9.14$^{**,++++}$
DBP (mm Hg)	89 ± 5.06	85 ±6.63^{++++}	92 ± 4.79	87 ± 7.85^{++++}	81 ± 6.00$^{**,++++}$	87 ± 4.71	86 ± 4.89^{+}	87 ± 6.26$^{+,+}$
MAP (mm Hg)	108 ± 4.66	100 ± 6.81**	112 ± 3.31	106 ± 7.94^{++++}	98 ± 9.11$^{*,++++}$	105 ± 3.73	103 ± 4.23^{++++}	101 ± 5.80$^{++++,++}$
HR (bpm)	75 ± 9.95	77 ± 8.03^{+}	76 ± 14.51	76 ± 10.33^{+}	75 ± 7.63$^{+,+}$	75 ± 7.68	75 ± 9.07^{+}	79 ± 8.41$^{++,+}$
24 – hour ABP (mean ± SD)								
-average 24-hour								
SBP (mm Hg)	140 ± 8.99	127 ± 12.85**	144 ± 6.03	139 ± 13.20^{+}	130 ± 16.07$^{++++,*}$	138 ± 10.18	132 ± 13.09^{+}	126 ± 11.69$^{**,+}$
DBP (mm Hg)	90 ± 10.19	79 ± 10.67*	92 ± 16.34	81 ± 11.40^{++}	81 ± 11.17$^{++,+}$	89 ± 6.02	79 ± 8.55^{++++}	78 ± 11.06$^{++++,+}$
MAP (mm Hg)	107 ± 7.93	95 ± 10.71**	109 ± 12.19	100 ± 11.44^{+}	98 ± 12.42$^{++,+++}$	105 ± 5.20	97 ± 9.70^{++++}	94 ± 10.36$^{*,+}$
HR (bpm)	79 ± 8.57	80 ± 6.52^{+}	84 ± 8.04	82 ± 4.27^{+}	82 ± 7.62$^{+,+}$	76 ± 7.86	77 ± 10.80^{+}	78 ± 5.96$^{+,+}$
- average day-time								
SBP (mm Hg)	143 ± 8.60	130 ± 12.89**	147 ± 6.85	141 ± 9.85^{+}	133 ± 14.93$^{++++,++++}$	141 ± 9.23	135 ± 12.19^{+}	127 ± 12.29$^{*,++}$
DBP (mm Hg)	92 ± 13.08	80 ± 11.30^{++++}	94 ± 15.26	81 ± 10.50^{+++}	83 ± 12.09$^{+,+}$	91 ± 12.90	82 ± 6.14^{++++}	79 ± 11.58$^{++++,+}$
MAP (mm Hg)	109 ± 9.97	97 ± 10.87*	112 ± 12.04	101 ± 9.09^{++}	100 ± 12.53$^{++,+}$	108 ± 9.41	100 ± 8.12^{++++}	95 ± 10.52$^{++++,+}$
HR (bpm)	82 ± 8.20	82 ± 6.34^{+}	87 ± 10.79	84 ± 3.87^{+}	84 ± 7.93$^{++,+}$	80 ± 6.00	80 ± 13.15^{+}	81 ± 5.50$^{+,+}$
- average night-time								
SBP (mm Hg)	131 ± 11.34	120 ± 15.44**	131 ± 7.93	129 ± 21.23^{+}	121 ± 20.63$^{++,*}$	131 ± 13.51	124 ± 14.06^{+}	119 ± 13.55$^{***,+}$
DBP (mm Hg)	81 ± 12.79	71 ± 8.18**	87 ± 17.21	78 ± 11.93^{+}	73 ± 8.58$^{++++,++++}$	78 ± 9.71	75 ± 11.82^{+}	70 ± 8.49$^{++++,++++}$
MAP (mm Hg)	98 ± 9.60	87 ± 9.54**	102 ± 11.39	95 ± 14.34^{+}	89 ± 11.00$^{++++,*}$	96 ± 8.97	91 ± 12.03^{+}	86 ± 9.41$^{**,++}$
HR (bpm)	69 ± 10.15	71 ± 10.93^{+}	71 ± 5.62	73 ± 5.32^{+}	76 ± 11.45$^{+,+}$	68 ± 12.29	66 ± 8.83^{+}	68 ± 10.60$^{+,+}$

a compared to baseline of each group, b compared to before combination of the second drug, *** p<0.001, ** p<0.01, *p<0.05, ++++ p=0.05-0.10, +++ p=0.11-0.20, ++ p=0.21-0.30, + p>0.31

Table 16: Office BP and 24-hour ABP of the subjects at baseline and after treatment with hydrochlorothiazide or $CaCO_3$ alone and when used the two drugs in combination (moderate hypertension based on office SBP/DBP at baseline)

Parameter	Baseline (n=14)	HCTZ + $CaCO_3$ (n=14) [a]	Group 1 (n=8)			Group 2 (n=7)		
			Baseline	HCTZ [a]	HCTZ + $CaCO_3$ [a,b]	Baseline	$CaCO_3$ [a]	$CaCO_3$ + HCTZ [a,b]
Office BP (mean ± SD)								
SBP (mm Hg)	161 ± 13.32	152 ± 16.64^{++++}	166 ± 12.31	145 ± 13.09***	147 ± 9.33$^{**,+}$	155 ± 12.74	158 ± 14.36^{+}	159 ± 22.14$^{+,+}$
DBP (mm Hg)	100 ± 9.10	92 ± 10.62**	96 ± 10.66	83 ± 7.25**	87 ± 11.22$^{++++,+++}$	105 ± 3.08	101 ± 4.51^{++++}	99 ± 5.13$^{*,+}$
MAP (mm Hg)	120 ± 5.98	112 ± 11.12**	120 ± 6.94	104 ± 8.47***	107 ± 10.02$^{**,++}$	121 ± 4.68	120 ± 6.91^{+}	119 ± 9.27$^{+,+}$
HR (bpm)	80 ± 8.24	78 ± 8.46^{++}	79 ± 10.38	79 ± 12.88^{+}	76 ± 7.65$^{++,+}$	80 ± 5.06	74 ± 5.43*	79 ± 9.93$^{+,+++}$
24 – hour ABP (mean ± SD)								
-average 24-hour								
SBP (mm Hg)	142 ± 14.35	139 ± 14.53^{+}	143 ± 11.67	130 ± 14.48*	134 ± 10.82$^{*,+}$	140 ± 18.37	146 ± 13.93^{++}	145 ± 17.65$^{+,+}$
DBP (mm Hg)	93 ± 12.71	83 ± 8.66*	94 ± 15.14	79 ± 16.52^{++++}	79 ± 6.05$^{*,+}$	92 ± 9.84	92 ± 11.71^{+}	89 ± 8.67$^{+,+}$
MAP (mm Hg)	110 ± 12.06	102 ±9.47*	110 ± 12.66	96 ± 14.83*	97 ± 5.37$^{**,+}$	108 ± 12.38	110 ± 11.29^{+}	107 ± 11.17$^{+,+}$
HR (bpm)	78 ± 10.40	75 ± 6.79^{+++}	77 ± 12.06	71 ± 11.65*	73 ± 7.57$^{++++,+}$	77 ± 8.82	76 ± 8.87^{+}	76 ± 5.81$^{+,+}$
- average day-time								
SBP (mm Hg)	143 ± 15.24	141 ± 15.65^{+}	144 ± 11.50	132 ± 12.38*	136 ± 11.61$^{++++,+}$	141 ± 20.28	147 ± 13.67^{+}	148 ± 18.95$^{+,+}$
DBP (mm Hg)	93 ± 12.40	86 ± 7.87^{++++}	95 ± 13.13	83 ± 16.92^{++++}	83 ± 5.12$^{*,+}$	92 ± 12.28	92 ± 11.18^{+}	90 ± 9.30$^{+,+}$
MAP (mm Hg)	110 ± 12.70	104 ± 9.47^{++++}	112 ± 11.72	99 ± 13.97*	101 ± 4.78$^{**,+}$	108 ± 14.48	110 ± 10.97^{+}	109 ± 12.14$^{+,+}$
HR (bpm)	80 ± 10.65	78 ± 7.08^{++}	80 ± 12.35	74 ± 13.61*	77 ± 8.80$^{++,+}$	81 ± 8.99	79 ± 7.50^{+}	79 ± 4.09$^{+,+}$
- average night-time								
SBP (mm Hg)	138 ± 13.02	133 ± 13.11^{++}	142 ± 12.09	126 ± 19.20*	131 ± 11.90$^{*,+}$	133 ± 13.59	143 ± 14.45^{+++}	136 ± 15.21$^{+,+}$
DBP (mm Hg)	89 ± 14.72	76 ± 11.53**	90 ± 19.28	73 ± 16.58*	71 ± 11.59$^{*,+}$	88 ± 6.28	88 ± 17.20^{+}	84 ± 6.47$^{++++,+}$
MAP (mm Hg)	105 ± 12.31	95 ± 10.21**	107 ± 15.55	91 ± 16.80*	91 ± 9.41$^{**,+}$	103 ± 6.52	106 ± 14.15^{+}	101 ± 8.42$^{+,+}$
HR (bpm)	65 ± 11.06	66 ± 10.53^{+}	67 ± 12.30	65 ± 12.59^{+++}	65 ± 11.41$^{+,+}$	63 ± 9.87	68 ± 10.07^{++++}	67 ± 10.23$^{++++,+}$

a compared to baseline of each group, b compared to before combination of the second drug, *** p<0.001, ** p<0.01, *p<0.05, ++++ p=0.05-0.10, +++ p=0.11-0.20, ++ p=0.21-0.30, + p>0.31

Parameter	Comparison of office BP and 24-hour ABP (mm Hg)											
	Mild hypertension (n=11)						Moderate hypertension (n=14)					
	Group 1 (n=4)			Group 2 (n=7)			Group 1 (n=8)			Group 2 (n=6)		
	HCTZ vs baseline (1)[a]	HCTZ+$CaCO_3$ vs baseline (2)[a]	(2)-(1)[b]	$CaCO_3$ vs baseline (3)[a]	CaCO3+HCTZ vs baseline (4)[a]	(4)-(3)[b]	HCTZ vs baseline (1)[a]	HCTZ+ $CaCO_3$ vs baseline (2)[a]	(2)-(1)[b]	$CaCO_3$ vs baseline (3)[a]	$CaCO_3$+HCTZ vs baseline (4)[b]	(4)-(3)[b]
Office BP												
BP (mm Hg)	$\downarrow 7^{***}$	$\downarrow 18^{++++}$	$\downarrow 11^{++++}$	$\downarrow 5^{++++}$	$\downarrow 15^{**}$	$\downarrow 10^{++++}$	$\downarrow 21^{***}$	$\downarrow 19^{**}$	$\uparrow 2^{+}$	$\uparrow 3^{+}$	$\uparrow 4^{+}$	$\uparrow 1^{+}$
DBP (mm Hg)	$\downarrow 5^{++++}$	$\downarrow 11^{**}$	$\downarrow 6^{++++}$	$\downarrow 1^{+}$	$\leftrightarrow^{+}$	$\uparrow 1^{+}$	$\downarrow 13^{**}$	$\downarrow 9^{++++}$	$\uparrow 4^{+++}$	$\downarrow 4^{++++}$	$\downarrow 6^{*}$	$\downarrow 2^{+}$
MAP (mm Hg)	$\downarrow 6^{++++}$	$\downarrow 14^{*}$	$\downarrow 8^{++++}$	$\downarrow 2^{++++}$	$\downarrow 4^{++++}$	$\downarrow 2^{++}$	$\downarrow 16^{***}$	$\downarrow 13^{**}$	$\uparrow 3^{++}$	$\downarrow 1^{+}$	$\downarrow 2^{+}$	$\downarrow 1^{+}$
24-hour ABP												
average 24-hour												
SBP (mm Hg)	$\downarrow 5^{+}$	$\downarrow 14^{++++}$	$\downarrow 9^{*}$	$\downarrow 6^{+}$	$\downarrow 12^{**}$	$\downarrow 6^{+}$	$\downarrow 13^{*}$	$\downarrow 9^{*}$	$\uparrow 4^{+}$	$\uparrow 6^{++}$	$\uparrow 5^{+}$	$\downarrow 1^{+}$
DBP (mm Hg)	$\downarrow 11^{++}$	$\downarrow 11^{++}$	$\leftrightarrow^{+}$	$\downarrow 10^{++++}$	$\downarrow 11^{++++}$	$\downarrow 1^{+}$	$\downarrow 15^{++++}$	$\downarrow 15^{*}$	$\leftrightarrow^{+}$	$\leftrightarrow^{+}$	$\downarrow 3^{+}$	$\downarrow 3^{+}$
MAP (mm Hg)	$\downarrow 9^{+}$	$\downarrow 11^{++}$	$\downarrow 2^{+++}$	$\downarrow 8^{++++}$	$\downarrow 11^{*}$	$\downarrow 3^{+}$	$\downarrow 14^{*}$	$\downarrow 13^{**}$	$\uparrow 1^{+}$	$\uparrow 2^{+}$	$\downarrow 1^{+}$	$\downarrow 3^{+}$
average day-time												
BP (mm Hg)	$\downarrow 6^{+}$	$\downarrow 14^{++++}$	$\downarrow 8^{++++}$	$\downarrow 6^{+}$	$\downarrow 14^{*}$	$\downarrow 8^{++}$	$\downarrow 12^{*}$	$\downarrow 8^{++++}$	$\uparrow 4^{+}$	$\uparrow 6^{+}$	$\uparrow 7^{+}$	$\uparrow 1^{+}$
DBP (mm Hg)	$\downarrow 13^{+++}$	$\downarrow 11^{+}$	$\uparrow 2^{+}$	$\downarrow 9^{++++}$	$\downarrow 12^{++++}$	$\downarrow 3^{+}$	$\downarrow 12^{++++}$	$\downarrow 12^{*}$	$\leftrightarrow^{+}$	$\leftrightarrow^{+}$	$\downarrow 2^{+}$	$\downarrow 2^{+}$
MAP (mm Hg)	$\downarrow 11^{++}$	$\downarrow 12^{++}$	$\downarrow 1^{+}$	$\downarrow 8^{++++}$	$\downarrow 13^{++++}$	$\downarrow 5^{+}$	$\downarrow 13^{*}$	$\downarrow 11^{**}$	$\uparrow 2^{+}$	$\uparrow 2^{+}$	$\uparrow 1^{+}$	$\downarrow 1^{+}$
verage night-time												
BP (mm Hg)	$\downarrow 2^{+}$	$\downarrow 10^{++}$	$\downarrow 8^{*}$	$\downarrow 7^{+}$	$\downarrow 12^{***}$	$\downarrow 5^{+}$	$\downarrow 16^{*}$	$\downarrow 11^{*}$	$\uparrow 5^{+}$	$\uparrow 10^{+++}$	$\uparrow 3^{+}$	$\downarrow 7^{+}$
BP (mm Hg)	$\downarrow 9^{+}$	$\downarrow 14^{++++}$	$\downarrow 5^{++++}$	$\downarrow 3^{+}$	$\downarrow 8^{++++}$	$\downarrow 5^{++++}$	$\downarrow 17^{*}$	$\downarrow 19^{*}$	$\downarrow 2^{+}$	$\leftrightarrow^{+}$	$\downarrow 4^{++++}$	$\downarrow 4^{+}$
AP (mm Hg)	$\downarrow 7^{+}$	$\downarrow 13^{++++}$	$\downarrow 6^{*}$	$\downarrow 5^{+}$	$\downarrow 10^{**}$	$\downarrow 5^{++}$	$\downarrow 16^{*}$	$\downarrow 16^{*}$	$\leftrightarrow^{+}$	$\uparrow 3^{+}$	$\downarrow 2^{+}$	$\downarrow 5^{+}$

compared to baseline of each group, b compared to before combination of the second drug

* p<0.001, ** p<0.01, *p<0.05, ++++ p=0.05-0.10, +++ p=0.11-0.20, ++ p=0.21-0.30, + p>0.31

When the patients were classified as dippers/non-dippers according to nocturnal reduction of baseline MAP, their office BP and 24-hour ABP reductions after treatment with HCTZ or $CaCO_3$ alone as compared to baseline and after combination treatment of the two drugs as compared to one drug were shown in Table 18. (Data of the office BP and 24-hour ABP reductions when the patients were classified as dippers/non-dippers according to nocturnal reduction of baseline SBP and DBP were demonstrated in Appendix O-P.)

HCTZ caused apparent reduction in office BP, 24-hour ABP, day-time and night-time BP in the dipper group when used alone. In the non-dipper group, after treatment with HCTZ alone, their office BP, 24 -hour ABP, day-time BP and night-time BP reductions from baseline all obviously less than the dipper group.

When $CaCO_3$ was used alone, non-dippers patients who were treated with $CaCO_3$ alone showed less reductions in their office BP and day-time BP as compared to dippers, however, night-time BP of the dippers even become higher than their baseline values, their accordingly 24-hour ABP therefore did not show higher reduction than those of the non-dippers.

After the second drug was added on the therapy in each group, when HCTZ had been used to combine with $CaCO_3$, further decrements in all types of BP were found in the dipper group with the increments of the reduction in DBP and MAP at night became statistically significant ($p<0.05$). However, for non-dipper group, only very small further reductions in night-time BP were found while the office BP, 24-hour ABP and day-time BP were pretty much the same as when $CaCO_3$ had been used alone.

Table 18: Comparison of office BP and 24- hour ABP after treatment with hydrochlorothiazide or $CaCO_3$ alone as compared to baseline and after combination of the two drugs as compared to one drug when the patients were classified as dippers/non-dippers according to nocturnal reduction of baseline MAP

Parameter	Comparison of office BP and 24-hour ABP (mm Hg)											
	Non-dipper (n=19)						Dipper (n=6)					
	Group 1 (n=10)			Group 2 (n=9)			Group 1 (n=2)			Group 2 (n=4)		
	HCTZ vs baseline (1)[a]	HCTZ+ $CaCO_3$ vs baseline (2)[a]	(2)-(1)[b]	$CaCO_3$ vs baseline (3)[a]	$CaCO_3$+HCTZ vs baseline (4)[a]	(4)-(3)[b]	HCTZ vs baseline (1)[a]	HCTZ+ $CaCO_3$ vs baseline (2)[a]	(2)-(1)[b]	$CaCO_3$ vs baseline (3)[a]	$CaCO_3$+HCTZ vs baseline (4)[b]	(4)-(3)[b]
Office BP												
SBP (mm Hg)	$\downarrow 14^{**}$	$\downarrow 16^{**}$	$\downarrow 2^{+}$	$\leftrightarrow^{+}$	$\downarrow 2^{+}$	$\downarrow 2^{+}$	$\downarrow 24^{++++}$	$\downarrow 34^{*}$	$\downarrow 10^{+}$	$\downarrow 4^{+}$	$\downarrow 14^{++++}$	$\downarrow 10^{+}$
DBP (mm Hg)	$\downarrow 12^{**}$	$\downarrow 11^{**}$	$\uparrow 1^{+}$	$\downarrow 2^{++}$	$\downarrow 1^{+}$	$\uparrow 1^{+}$	$\downarrow 3^{+}$	$\downarrow 4^{+}$	$\downarrow 1^{+}$	$\downarrow 3^{++}$	$\downarrow 7^{*}$	$\downarrow 4^{++}$
MAP (mm Hg)	$\downarrow 13^{***}$	$\downarrow 13^{***}$	$\leftrightarrow^{+}$	$\downarrow 1^{++}$	$\downarrow 1^{+}$	$\leftrightarrow^{+}$	$\downarrow 10^{++++}$	$\downarrow 14^{++}$	$\downarrow 4^{+}$	$\downarrow 3^{+}$	$\downarrow 9^{*}$	$\downarrow 6^{+++}$
24-hour ABP												
-average 24-hour												
SBP (mm Hg)	$\downarrow 8^{++++}$	$\downarrow 8^{*}$	$\leftrightarrow^{+}$	$\leftrightarrow^{+}$	$\uparrow 1^{+}$	$\uparrow 1^{+}$	$\downarrow 18^{++++}$	$\downarrow 22^{++++}$	$\downarrow 4^{+}$	$\downarrow 3^{+}$	$\downarrow 18^{**}$	$\downarrow 15^{+++}$
DBP (mm Hg)	$\downarrow 12^{++++}$	$\downarrow 14^{*}$	$\downarrow 2^{+}$	$\downarrow 6^{++++}$	$\downarrow 6^{++}$	$\leftrightarrow^{+}$	$\downarrow 17^{+}$	$\downarrow 11^{+}$	$\uparrow 6^{+}$	$\downarrow 3^{+}$	$\downarrow 11^{++++}$	$\downarrow 8^{+++}$
MAP (mm Hg)	$\downarrow 11^{++++}$	$\downarrow 12^{**}$	$\downarrow 1^{+}$	$\downarrow 4^{++}$	$\downarrow 4^{+}$	$\leftrightarrow^{+}$	$\downarrow 18^{++}$	$\downarrow 15^{+}$	$\uparrow 3^{+}$	$\downarrow 3^{+}$	$\downarrow 14^{*}$	$\downarrow 11^{+++}$
-average day-time												
SBP (mm Hg)	$\downarrow 9^{++++}$	$\downarrow 8^{*}$	$\uparrow 1^{+}$	$\uparrow 2^{+}$	$\uparrow 3^{+}$	$\uparrow 1^{+}$	$\downarrow 18^{++++}$	$\downarrow 22^{++}$	$\downarrow 4^{+}$	$\downarrow 5^{+}$	$\downarrow 21^{**}$	$\downarrow 16^{+++}$
DBP (mm Hg)	$\downarrow 10^{++++}$	$\downarrow 11^{*}$	$\downarrow 1^{+}$	$\downarrow 2^{+}$	$\downarrow 2^{+}$	$\leftrightarrow^{+}$	$\downarrow 22^{++}$	$\downarrow 15^{+}$	$\uparrow 7^{+}$	$\downarrow 9^{+}$	$\downarrow 19^{++++}$	$\downarrow 10^{+++}$
MAP (mm Hg)	$\downarrow 10^{++++}$	$\downarrow 10^{*}$	$\leftrightarrow^{+}$	$\downarrow 1^{+}$	$\leftrightarrow^{+}$	$\uparrow 1^{+}$	$\downarrow 21^{++++}$	$\downarrow 18^{+}$	$\uparrow 3^{+}$	$\downarrow 8^{+}$	$\downarrow 20^{*}$	$\downarrow 12^{++++}$
-average night-time												
SBP (mm Hg)	$\downarrow 9^{++++}$	$\downarrow 9^{*}$	$\leftrightarrow^{+}$	$\downarrow 1^{+}$	$\downarrow 4^{+}$	$\downarrow 3^{+}$	$\downarrow 20^{++++}$	$\downarrow 19^{++++}$	$\uparrow 1^{+}$	$\uparrow 4^{+}$	$\downarrow 8^{++++}$	$\downarrow 12^{+++}$
DBP (mm Hg)	$\downarrow 13^{++++}$	$\downarrow 18^{**}$	$\downarrow 5^{++}$	$\downarrow 5^{+}$	$\downarrow 7^{*}$	$\downarrow 2^{+}$	$\downarrow 17^{+}$	$\downarrow 14^{+}$	$\uparrow 3^{+}$	$\uparrow 7^{++++}$	$\downarrow 5^{+}$	$\downarrow 12^{*}$
MAP (mm Hg)	$\downarrow 12^{++++}$	$\downarrow 15^{**}$	$\downarrow 3^{+}$	$\downarrow 4^{+}$	$\downarrow 6^{++++}$	$\downarrow 2^{+}$	$\downarrow 18^{+++}$	$\downarrow 15^{+}$	$\uparrow 3^{+}$	$\uparrow 6^{++}$	$\downarrow 6^{+++}$	$\downarrow 12^{*}$

a compared to baseline of each group, b compared to before combination of the second drug, *** p<0.001, ** p<0.01, *p<0.05, ++++ p=0.05-0.10, +++ p=0.11-0.20, ++ p=0.21-0.30, + p>0.31

$CaCO_3$ added on to HCTZ caused only small further reduction in night-time DBP in the non-dipper group which is not statistically significant (p=0.21-0.30), while no further reduction any other types of BP could be found. However, for dippers, $CaCO_3$ added on to HCTZ could cause only small further reduction in SBP while their DBP reduction even become less than that obtained when the single drug had been used, besides, all of these difference were not statistically significant (p>0.31).

4.2 Therapeutic effects of HCTZ and $CaCO_3$ on blood pressure loads

Table 19 showed the frequency (percentage) of BP loads at baseline and after treatment with each of the two regimens. Only the regimen which started with HCTZ (group 1) showed significant reductions in the frequency of SBP loads (percentage of abnormal BP values) in comparison to baseline whether the values were considered for day-time BP only, night-time BP only or when the whole 24-hour BP were taken into consideration (p<0.05). The reductions in SBP loads were significant different from baseline whether HCTZ was used alone or used in combination with $CaCO_3$ (p<0.01) (Table 20).

In contrary, for patients who started their regimens with $CaCO_3$ (group 2) neither day-time BP, night-time BP or 24-hour BP frequency of any BP loads were significantly reduced from baseline when $CaCO_3$ was used as a single drug. However, when HCTZ was added to the regimen, only night-time DBP loads was significantly reduced from baseline (p<0.01) while none of the other BP loads were significantly different from baseline. After the second drug had been combined for another 4 weeks, the second drug did not induce any further reduction in either SBP or DBP loads which were statistically significant different in both groups (Table 19-20).

Table 19: Frequency of BP load (%) of the subjects at baseline and after treatment with hydrochlorothiazide or $CaCO_3$ alone and when used the two drugs in combination

	Frequency of BP load (%)							
	Baseline (n=25)	HCTZ + $CaCO_3$ (n=25) [a]	Group 1 (n=12)			Group 2 (n=13)		
			Baseline	HCTZ [a]	HCTZ + $CaCO_3$ [a,b]	Baseline	$CaCO_3$ [a]	$CaCO_3$ + HCTZ [a,b]
24-hour BP load (mean ± SD)								
SBP	51 ± 22.81	39 ± 23.96*	60 ± 17.49	40 ± 28.94*	36 ± 18.52$^{***,+}$	43 ± 24.79	43 ± 25.15^{+}	40 ± 28.73$^{+,+}$
DBP	48 ± 34.07	30 ± 22.15*	51 ± 36.07	27 ± 29.18^{++++}	26 ± 20.80$^{++++,+}$	44 ± 33.21	39 ± 27.06^{+}	34 ± 23.48$^{+,+}$
Day-time BP load (mean ± SD)								
SBP	56 ± 23.91	42 ± 24.21*	62 ± 20.20	46 ± 27.52^{++++}	39 ± 17.69$^{***,+}$	50 ± 26.26	46 ± 23.87^{+}	45 ± 29.51$^{+,+}$
DBP	48 ± 32.12	35 ± 24.85^{++++}	54 ± 35.20	31 ± 26.87^{++++}	31 ± 22.61$^{++++,+}$	42 ± 29.26	41 ± 25.58^{+}	38 ± 27.27$^{+,+}$
Night-time BP load (mean ± SD)								
SBP	79 ± 26.66	64 ± 33.99*	88 ± 18.95	63 ± 38.08**	67 ± 35.86$^{**,+}$	70 ± 30.35	75 ± 27.35^{+}	61 ± 33.29$^{+,++++}$
DBP	58 ± 34.82	37 ± 32.89**	58 ± 41.71	45 ± 44.75^{+}	33 ± 36.24$^{*,++++}$	59 ± 28.79	53 ± 43.41^{+}	39 ± 30.69$^{**,++++}$

a compared to baseline of each group, b compared to before combination of the second drug

*** p<0.001, ** p<0.01, *p<0.05, ++++ p=0.05-0.10, +++ p=0.11-0.20, ++ p=0.21-0.30, + p>0.31

Table 20: Comparison of frequency of BP load (%) of the subjects at baseline and after treatment with hydrochlorothiazide or $CaCO_3$ alone and after combination of the two drugs as compared to one drugs

	Comparison of frequency of BP load (%)					
	Group 1 (n=12)			Group 2 (n=13)		
	HCTZ vs baseline[a] (1)	HCTZ + $CaCO_3$ vs baseline[a] (2)	(2) – (1)[b]	$CaCO_3$ vs baseline[a] (3)	$CaCO_3$ + HCTZ vs baseline[a] (4)	(4) – (3)[b]
24-hour BP load						
SBP	$\downarrow 20^{*}$	$\downarrow 24^{***}$	$\downarrow 4^{+}$	$\uparrow 0.08^{+}$	$\downarrow 3^{+}$	$\downarrow 3^{+}$
DBP	$\downarrow 24^{++++}$	$\downarrow 25^{++++}$	$\downarrow 1^{+}$	$\downarrow 5^{+}$	$\downarrow 10^{+}$	$\downarrow 5^{+}$
Day-time BP load						
SBP	$\downarrow 16^{++++}$	$\downarrow 23^{***}$	$\downarrow 7^{+}$	$\downarrow 4^{+}$	$\downarrow 5^{+}$	$\downarrow 1^{+}$
DBP	$\downarrow 23^{++++}$	$\downarrow 23^{++++}$	$\uparrow 0.50^{+}$	$\downarrow 1^{+}$	$\downarrow 4^{+}$	$\downarrow 3^{+}$
Night-time BP load						
SBP	$\downarrow 25^{**}$	$\downarrow 21^{**}$	$\uparrow 4^{+}$	$\uparrow 5^{+}$	$\downarrow 9^{+}$	$\downarrow 14^{++++}$
DBP	$\downarrow 13^{+}$	$\downarrow 25^{*}$	$\downarrow 12^{++++}$	$\downarrow 6^{+}$	$\downarrow 20^{**}$	$\downarrow 14^{++++}$

a compared to baseline of each group, b compared to before combination of the second drug

*** p<0.001, ** p<0.01, *p<0.05, ++++ p=0.05-0.10, +++ p=0.11-0.20, ++ p=0.21-0.30, + p>0.31

When patients were classified as mild and moderate hypertension groups, BP loads of mild hypertensive patients who were treated with HCTZ 25 mg OD or $CaCO_3$ 1 gm BID alone for 4 weeks were not statistically significant dropped from baseline ($p>0.05$). After the second drugs had been combined for another 4 weeks in either regimen the BP loads were further decreased from treatment with HCTZ or $CaCO_3$ alone and were statistically significantly different from baseline especially in group 2 at $p<0.05$ ($CaCO_3$ first then combined with HCTZ) (Table 21, 23).

For moderate hypertension, SBP loads during day-time, night-time and whole 24-hour were significantly reduced ($p<0.01$) after using HCTZ 25 mg alone for 4 weeks, addition of $CaCO_3$ did not cause any further significant reduction in any of BP loads ($p>0.31$). At the same time, neither types of BP loads day-time, night-time or whole 24-hour were increased after treatment with $CaCO_3$ 1 gm BID or even when HCTZ had been added (Table 22-23).

BP loads was used as one parameter to assess the antihypertensive efficacy of the medication. In this study, for group 1 patients significant reduction of the percentage of abnormal BP values especially SBP loads occurred during night-time and the whole 24-hour BP after treatment with either HCTZ 25 mg OD alone or after combined with $CaCO_3$ 1 gm BID ($p<0.05$). However, during day-time significant reduction in the percentage of abnormal BP values occurred only after $CaCO_3$ 1 gm BID had been combined ($p<0.001$). In contrast, with group 2 regimen significant reduction of the percentage of night-time loads of DBP occurred only after combined HCTZ 25 mg for another 4 weeks ($p<0.01$) (Table 19).

Table 21: Frequency of BP load (%) of the subjects at baseline and after treatment with hydrochlorothiazide or $CaCO_3$ alone and when used the two drugs in combination

(mild hypertension based on office SBP/DBP at baseline)

	Frequency of BP load (%)							
	Baseline (n=11)	HCTZ + $CaCO_3$ (n=11)[a]	Group 1 (n=4)			Group 2 (n=7)		
			Baseline	HCTZ[a]	HCTZ + $CaCO_3$[a,b]	Baseline	$CaCO_3$[a]	$CaCO_3$ + HCTZ[a,b]
24-hour BP load (mean ± SD)								
SBP	46 ± 19.31	32 ± 20.43*	56 ± 18.63	60 ± 26.73^{+}	35 ± 21.75$^{++++,++++}$	41 ± 18.99	34 ± 21.80^{+}	30 ± 21.26$^{++++,+}$
DBP	46 ± 36.40	26 ± 20.99^{++++}	49 ± 41.71	35 ± 25.59^{+}	34 ± 28.66$^{+,+}$	44 ± 36.48	22 ± 11.98^{++++}	22 ± 16.03$^{++++,+}$
Day-time BP load (mean ± SD)								
SBP	57 ± 20.02	35 ± 18.96**	65 ± 21.93	65 ± 24.01^{+}	37 ± 20.34$^{++++,++++}$	52 ± 19.05	37 ± 21.16^{++}	33 ± 19.68$^{*,+}$
DBP	44 ± 31.91	30 ± 22.33^{++}	52 ± 40.65	35 ± 21.95^{+}	39 ± 29.81$^{+,+}$	39 ± 28.41	26 ± 14.35^{+}	25 ± 17.48$^{++,+}$
Night-time BP load (mean ± SD)								
SBP	76 ± 24.38	50 ± 36.40**	80 ± 25.37	70 ± 41.99^{+}	56 ± 52.16$^{++,++}$	73 ± 25.43	57 ± 25.41^{++}	46 ± 28.46$^{**,+}$
DBP	46 ± 33.75	25 ± 29.46*	48 ± 44.61	52 ± 48.52^{+}	36 ± 44.82$^{+,++}$	44 ± 29.93	34 ± 39.84^{+}	19 ± 18.04$^{**,+}$

a compared to baseline of each group, b compared to before combination of the second drug

*** p<0.001, ** p<0.01, *p<0.05, ++++ p=0.05-0.10, +++ p=0.11-0.20, ++ p=0.21-0.30, + p>0.31

Table 22: Frequency of BP load (%) of the subjects at baseline and after treatment with hydrochlorothiazide or $CaCO_3$ alone and when used the two drugs in combination (moderate hypertension based on office SBP/DBP at baseline)

	Frequency of BP load (%)							
	Baseline (n=14)	HCTZ + $CaCO_3$ (n=14)[a]	Group 1 (n=8)			Group 2 (n=6)		
			Baseline	HCTZ[a]	HCTZ + $CaCO_3$[a,b]	Baseline	$CaCO_3$[a]	$CaCO_3$ + HCTZ[a,b]
24-hour BP load (mean ± SD)								
SBP	54 ± 25.35	44 ± 25.93^{+++}	62 ± 17.82	30 ± 25.72**	37 ± 18.24$^{***,+}$	45 ± 32.13	53 ± 26.13^{++}	52 ± 33.60$^{+,+}$
DBP	49 ± 33.44	34 ± 23.28^{++++}	53 ± 35.96	22 ± 31.61^{++++}	22 ± 16.49$^{++++,+}$	44 ± 32.40	57 ± 27.84^{+++}	48 ± 23.35$^{+,+}$
Day-time BP load (mean ± SD)								
SBP	55 ± 27.31	48 ± 26.91^{+}	61 ± 20.73	36 ± 24.79**	41 ± 17.60$^{**,+}$	47 ± 34.65	56 ± 24.35^{+}	58 ± 35.28$^{+,+}$
DBP	51 ± 33.16	38 ± 26.96^{++}	55 ± 35.14	29 ± 30.26^{++++}	27 ± 19.23$^{++++,+}$	45 ± 32.64	58 ± 25.57^{+++}	52 ± 30.57$^{+,+}$
Night-time BP load (mean ± SD)								
SBP	82 ± 28.95	75 ± 28.25^{+}	92 ± 15.25	60 ± 38.58**	73 ± 27.03$^{*,++}$	67 ± 37.58	95 ± 8.82^{++++}	77 ± 32.23$^{+,++}$
DBP	69 ± 33.30	45 ± 33.81*	63 ± 42.47	42 ± 45.84^{+++}	32 ± 34.61$^{++++,+}$	77 ± 14.47	75 ± 38.87^{+}	62 ± 25.72$^{++,+}$

a compared to baseline of each group, b compared to before combination of the second drug

*** p<0.001, ** p<0.01, *p<0.05, ++++ p=0.05-0.10, +++ p=0.11-0.20, ++ p=0.21-0.30, + p>0.31

Table 23: Comparison of frequency of BP loads (%) after treatment with hydrochlorothiazide or $CaCO_3$ alone as compared to baseline and after combination of the two drugs as compared to one drug (mild/moderate hypertension based on office SBP/DBP at baseline)

	Comparison of frequency of BP loads (%)											
	Mild hypertension (n=11)						Moderate hypertension (n=14)					
	Group 1 (n=4)			Group 2 (n=7)			Group 1 (n=8)			Group 2 (n=6)		
	HCTZ vs baseline (1)[a]	HCTZ+ $CaCO_3$ vs baseline (2)[a]	(2)-(1)[b]	$CaCO_3$ vs baseline (3)[a]	$CaCO_3$+HCTZ vs baseline (4)[a]	(4)-(3)[b]	HCTZ vs baseline (1)[a]	HCTZ+ $CaCO_3$ vs baseline (2)[a]	(2)-(1)[b]	$CaCO_3$ vs baseline (3)[a]	$CaCO_3$+HCTZ vs baseline (4)[b]	(4)-(3)[b]
24-hour BP loads												
SBP	$\uparrow 4^{+}$	$\downarrow 21^{++++}$	$\downarrow 25^{++++}$	$\downarrow 7^{+}$	$\downarrow 11^{++++}$	$\downarrow 4^{+}$	$\downarrow 32^{**}$	$\downarrow 25^{***}$	$\uparrow 7^{+}$	$\uparrow 8^{++}$	$\uparrow 7^{+}$	$\downarrow 1^{+}$
DBP	$\downarrow 14^{+}$	$\downarrow 15^{+}$	$\downarrow 1^{+}$	$\downarrow 22^{++++}$	$\downarrow 22^{++++}$	$\leftrightarrow^{+}$	$\downarrow 31^{++++}$	$\downarrow 31^{++++}$	$\leftrightarrow^{+}$	$\uparrow 13^{+++}$	$\uparrow 4^{+}$	$\downarrow 9^{+}$
Day-time BP loads												
SBP	$\leftrightarrow^{+}$	$\downarrow 28^{++++}$	$\downarrow 28^{++++}$	$\downarrow 15^{++}$	$\downarrow 19^{*}$	$\downarrow 4^{+}$	$\downarrow 25^{**}$	$\downarrow 20^{**}$	$\uparrow 5^{+}$	$\uparrow 9^{+}$	$\uparrow 11^{+}$	$\uparrow 2^{+}$
DBP	$\downarrow 17^{+}$	$\downarrow 13^{+}$	$\uparrow 4^{+}$	$\downarrow 13^{+}$	$\downarrow 14^{++}$	$\downarrow 1^{+}$	$\downarrow 26^{++++}$	$\downarrow 28^{++++}$	$\downarrow 2^{+}$	$\uparrow 13^{+++}$	$\uparrow 7^{+}$	$\downarrow 6^{+}$
Night-time BP loads												
SBP	$\downarrow 10^{+}$	$\downarrow 24^{++}$	$\downarrow 14^{++}$	$\downarrow 16^{++}$	$\downarrow 27^{**}$	$\downarrow 11^{+}$	$\downarrow 32^{**}$	$\downarrow 19^{*}$	$\uparrow 13^{++}$	$\uparrow 28^{++++}$	$\uparrow 10^{+}$	$\downarrow 18^{++}$
DBP	$\uparrow 4^{+}$	$\downarrow 12^{+}$	$\downarrow 16^{++}$	$\downarrow 10^{+}$	$\downarrow 25^{**}$	$\downarrow 15^{+}$	$\downarrow 21^{+++}$	$\downarrow 31^{++++}$	$\downarrow 10^{+}$	$\downarrow 2^{+}$	$\downarrow 15^{++}$	$\downarrow 13^{+}$

a compared to baseline of each group, b compared to before combination of the second drug

*** p<0.001, ** p<0.01, *p<0.05, ++++ p=0.05-0.10, +++ p=0.11-0.20, ++ p=0.21-0.30, + p>0.31

When patients were classified as dippers/non-dippers according to nocturnal reduction of baseline MAP, reduction in frequency of BP loads (%) after treatment with HCTZ or $CaCO_3$ alone as compared to baseline and after combination of two drugs as compared to one drug were shown in Table 24. (The reduction in frequency of BP load (%) when the patients were classified as dipper/non-dippers according to nocturnal reduction of baseline SBP and DBP were demonstrated in detail in Appendix Q-R.)

In the dipper group, after treatment with HCTZ or $CaCO_3$ alone, their percentage of BP loads were mostly decreased from baseline in a higher percentage than the non-dipper group ($p>0.05$), except for the percentage of night-time DBP load after treatment with $CaCO_3$ alone which the non-dipper group showed higher decrement from baseline than the dipper group.

After $CaCO_3$ was added on as the second drug to the therapy with HCTZ, small increment in the percentage of reduction in all types of BP load were found in the non-dipper group while in the dipper group, only the percentage of SBP load reduction during day-time and their accordingly 24-hour SBP were increased after $CaCO_3$ was added on to combine with HCTZ as compared to treatment with HCTZ alone ($p<0.05$ and $p<0.01$, respectively).

When HCTZ had been added on to combine with $CaCO_3$ for 4 weeks, there were further increment in the percentage of BP loads reduction all types of BP in the dipper group ($p>0.31$) while in the non-dipper group only the percentage of night-time BP loads was further reduced ($p=0.21$-0.30).

The 24-hour ABP profile after both regimen (Group 1 were assigned to receive HCTZ 25 mg OD combined with placebo of $CaCO_3$ 1 gm BID for 4 weeks and then combined

Table 24: Comparison of frequency of BP loads (%) after treatment with hydrochlorothiazide or $CaCO_3$ alone as compared to baseline and after combination of the two drugs as compared to one drug when patients were classified as dippers/non-dippers according to nocturnal reduction of baseline MAP

	Comparison of frequency of BP loads (%)											
	Non-dipper (n=19)						Dipper (n=6)					
	Group 1 (n=10)			Group 2 (n=9)			Group 1 (n=2)			Group 2 (n=4)		
	HCTZ vs baseline (1)[a]	HCTZ+ $CaCO_3$ vs baseline (2)[a]	(2)-(1)[b]	$CaCO_3$ vs baseline (3)[a]	$CaCO_3$+HCTZ vs baseline (4)[a]	(4)-(3)[b]	HCTZ vs baseline (1)[a]	HCTZ+ $CaCO_3$ vs baseline (2)[a]	(2)-(1)[b]	$CaCO_3$ vs baseline (3)[a]	$CaCO_3$+HCTZ vs baseline (4)[b]	(4)-(3)[b]
24-hour BP loads												
SBP	$\downarrow 18^{+++}$	$\downarrow 21^{**}$	$\downarrow 3^{+}$	$\uparrow 4^{+}$	$\uparrow 6^{+}$	$\uparrow 2^{+}$	$\downarrow 32^{++}$	$\downarrow 38^{*}$	$\downarrow 6^{+}$	$\downarrow 9^{+}$	$\downarrow 22^{*}$	$\downarrow 13^{+}$
DBP	$\downarrow 21^{+++}$	$\downarrow 24^{++++}$	$\downarrow 3^{+}$	$\downarrow 4^{+}$	$\downarrow 2^{+}$	$\uparrow 2^{+}$	$\downarrow 41^{+}$	$\downarrow 31^{+}$	$\uparrow 10^{+}$	$\downarrow 9^{+}$	$\downarrow 29^{++++}$	$\downarrow 20^{++}$
Day-time BP loads												
SBP	$\downarrow 13^{++}$	$\downarrow 19^{**}$	$\downarrow 6^{+}$	$\downarrow 1^{+}$	$\uparrow 5^{+}$	$\uparrow 6^{+}$	$\downarrow 32^{+}$	$\downarrow 42^{**}$	$\downarrow 10^{+}$	$\downarrow 12^{+}$	$\downarrow 28^{*}$	$\downarrow 16^{+}$
DBP	$\downarrow 19^{+++}$	$\downarrow 22^{++++}$	$\downarrow 3^{+}$	$\uparrow 3^{+}$	$\uparrow 8^{+}$	$\uparrow 5^{+}$	$\downarrow 44^{++}$	$\downarrow 27^{+}$	$\uparrow 17^{+}$	$\downarrow 9^{+}$	$\downarrow 34^{++++}$	$\downarrow 25^{+++}$
Night-time BP loads												
SBP	$\downarrow 21^{*}$	$\downarrow 18^{++++}$	$\uparrow 3^{+}$	$\uparrow 8^{+}$	$\downarrow 7^{+}$	$\downarrow 15^{++}$	$\downarrow 44^{+++}$	$\downarrow 36^{+++}$	$\uparrow 8^{+}$	$\downarrow 3^{+}$	$\downarrow 14^{+}$	$\downarrow 11^{+}$
DBP	$\downarrow 8^{+}$	$\downarrow 23^{++++}$	$\downarrow 15^{+++}$	$\downarrow 11^{+}$	$\downarrow 25^{**}$	$\downarrow 14^{++}$	$\downarrow 36^{+}$	$\downarrow 30^{+}$	$\uparrow 6^{+}$	$\uparrow 6^{+}$	$\downarrow 8^{+}$	$\downarrow 14^{+}$

a compared to baseline of each group, b compared to before combination of the second drug

*** p<0.001, ** p<0.01, *p<0.05, ++++ p=0.05-0.10, +++ p=0.11-0.20, ++ p=0.21-0.30, + p>0.31

with $CaCO_3$ 1 gm BID instead of placebo, the other group 2 were assigned to receive $CaCO_3$ 1 gm BID combined with placebo of HCTZ 25 mg OD for 4 weeks and then combined with HCTZ 25 mg OD instead of placebo) were shown in Figure 19-20. The result demonstrated that BP were reduced for both SBP and DBP throughout 24 hour. Group 1 therapy showed a consistency blood pressure control throughout the 24-hour profile while group 2 therapy showed only small reduction in BP after $CaCO_3$ alone but after combined with HCTZ a better control BP was illustrated especially during night-time.

Table 25 illustrated the effects of treatment on the numbers and the percentage of normalized and responded subjects based on office and 24-hour ambulatory blood pressure (24-ABP).

When patients were categorized as normalized and non-normalized groups according to their office BP (patients whose office SBP/DBP <140/90 mm Hg were categorized as normalized patients), it was found that the percentage of normalized patients after treatment with HCTZ and $CaCO_3$ alone were 42% and 23%, respectively. When classified the patients into responder and non-responder groups (patients whose their office SBP or DBP decreased $\geq$ 10% after treatment with each regimen were classified as responder), the percentage of responded patients after HCTZ alone was 67% while after $CaCO_3$ alone treatment was 8%.

When patients were classified based on their 24-hour ambulatory blood pressure into normalized/non-normalized and responder/non-responder groups (patients whose 24-hour SBP/DBP $\leq$ 130/80 mm Hg were categorized as normalized subjects and patients whose 24-hour SBP or DBP decreased $\geq$ 10% after treatment with each regimen were categorized as responded

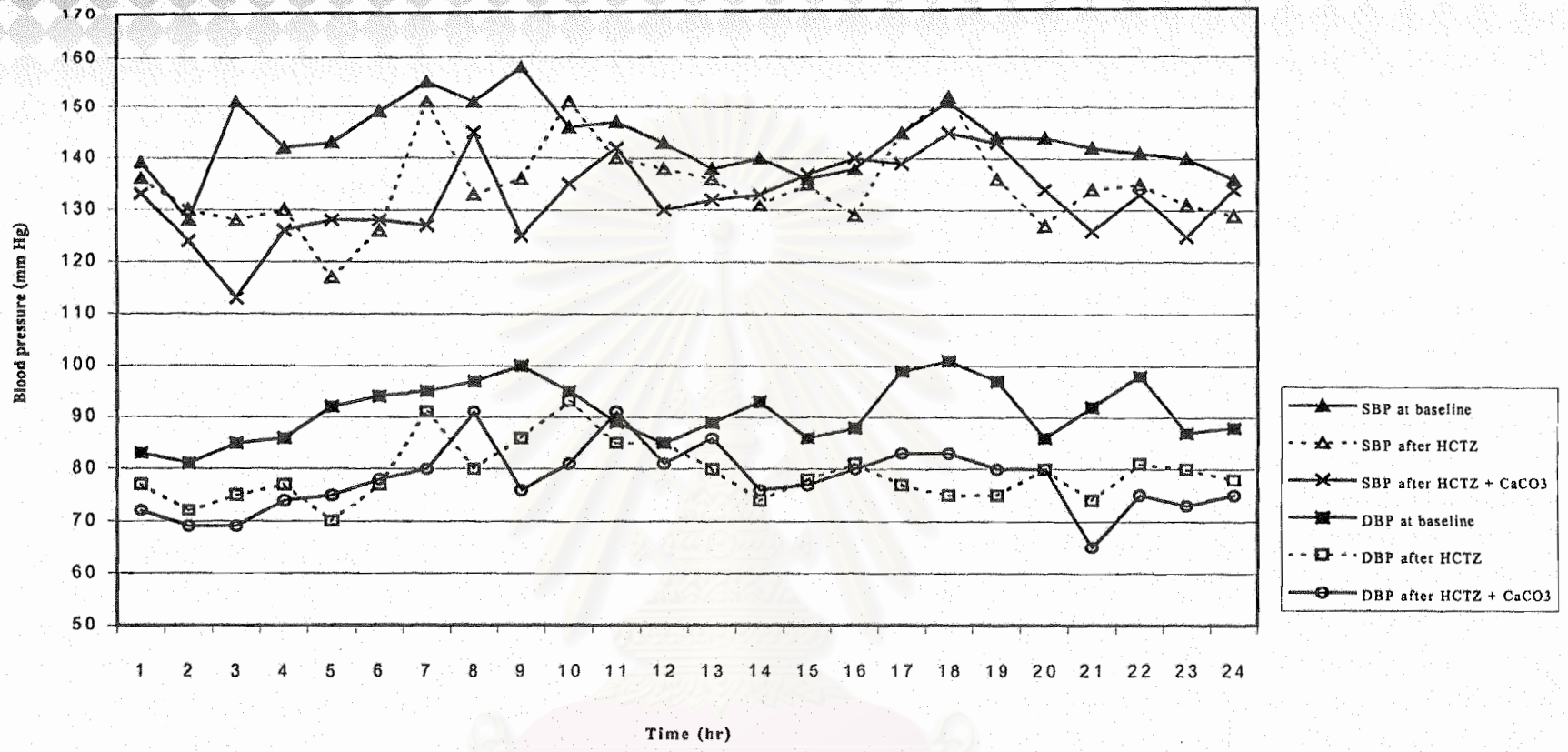

Figure 19: Ambulatory Hourly Blood Pressure data of subjects group 1 at baseline, after treatment with HCTZ alone for 4 weeks and after combined with $CaCO_3$ for another 4 weeks (n=12)

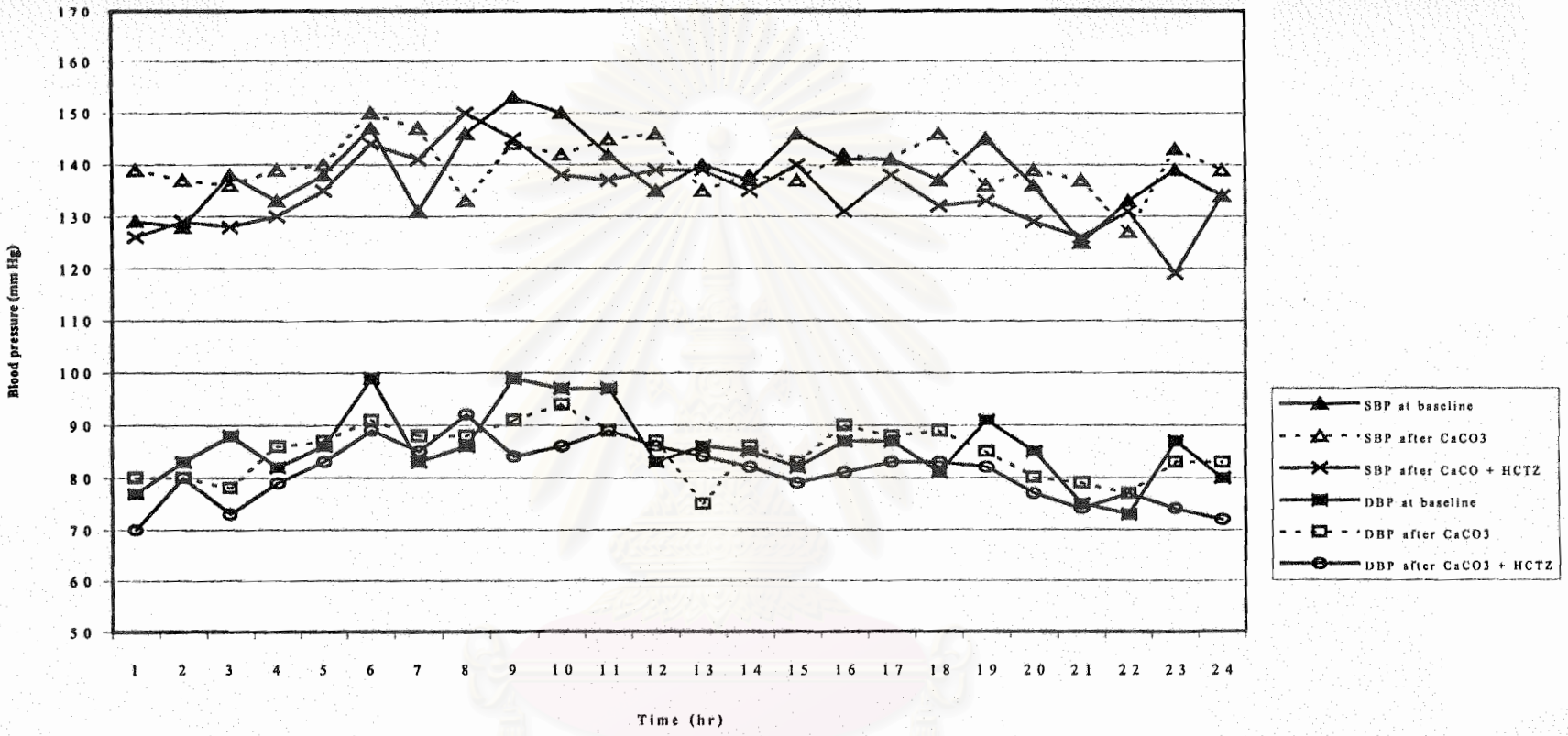

Figure 20: Ambulatory Hourly Blood Pressure data of subjects group 2 at baseline, after treatment with $CaCO_3$ alone for 4 weeks and after combined with HCTZ for another 4 weeks (n=13)

Table 25: The effects of treatment on the numbers and the percentage of normalized and responded subjects based on office and 24-hour ambulatory blood pressure (24-ABP) (n=25)

		Office blood pressure (OBP)			24-Ambulatory blood pressure (24-ABP)	
		Single drug	Combination drugs		Single drug	Combination drugs
(HCTZ 25 mg OD)				(HCTZ 25 mg OD)		
Normalized [a]				Normalized [c]		
	N	(5/12)	(4/12)	N	(5/12)	(4/12)
	%	42	33	%	42	33
Responder [b]				Responder [d]		
	N	(8/12)	(10/12)	N	(8/12)	(10/12)
	%	67	83	%	67	83
($CaCO_3$ 1 gm BID)				($CaCO_3$ 1 gm BID)		
Normalized [a]				Normalized [c]		
	N	(3/13)	(6/13)	N	(3/13)	(6/13)
	%	23	46	%	23	46
Responder [b]				Responder [d]		
	N	(1/13)	(6/13)	N	(6/13)	(7/13)
	%	8	46	%	46	54

a= OSBP<140 and DBP<90 mm Hg after treatment

b= OSBP or ODBP reduction of $\geq$ 10% from baseline after treatment

c= 24-hour SBP $\leq$ 130 and 24-hour DBP $\leq$ 80 mm Hg after treatment

d= 24-hour SBP or 24-hour DBP reduction of $\geq$ 10% from baseline after treatment

patients), it was found that the percentage of normalized and responders either after HCTZ alone or after $CaCO_3$ alone treatments were similar will be the percentages obtained by using the office blood pressure except for the percentage of responder after $CaCO_3$ alone treatments which was 46% and was higher than the percentage of responder obtained by using the office blood pressure. Considering on the effect of treatment, it was found that, the percentage of normalized and responders of the drug seem to be higher when the second drug has been given (group 1 plus $CaCO_3$ 1 gm BID instead of placebo and group 2 plus HCTZ 25 mg instead of placebo), however, these were all non statistically significant.

When patients were classified as mild and moderate hypertension groups, in mild hypertensive patients, the percentage of normalized patients based on their 24-hour ABP, after treatment with HCTZ and $CaCO_3$ alone were 25% and 43% while moderate hypertensive patients were 50% and 0%, respectively. After the second drug has been given in each regimen, the increment of the percentage of normalized were found with both regimens in mild hypertensive patients, the percentage of normalized increased to 50% and 71% for the first and the second regimen, respectively. In moderate hypertension group, addition of $CaCO_3$ to the patients who had already taken HCTZ 25 mg did not add any further improvement in their blood pressure if not drawback, while adding HCTZ to the existing $CaCO_3$ treatment could slightly increase the percentage of normalized (Table 26).

When patients were categorized as responder and non-responder groups, the percentage of responded patients after treatment with HCTZ and $CaCO_3$ alone in mild hypertension group were 50% and 71% while in moderate group were 75% and 17%. Considering

Table 26: The effects of treatment on the numbers and the percentage of normalized and responded subjects based on office and 24-hour ambulatory blood pressure (compared between mild and moderate hypertensive patients)

	Office blood pressure (OBP)			24-Ambulatory blood pressure (24-ABP)	
	Single drug	Combination drugs		Single drug	Combination drugs
(HCTZ 25 mg OD)			(HCTZ 25 mg OD)		
Normalized [a]			Normalized [c]		
Mild	2/4 (50%)	2/4 (50%)	Mild	1/4 (25%)	2/4 (50%)
Moderate	3/8 (38%)	2/8 (25%)	Moderate	4/8 (50%)	2/8 (25%)
Responder [b]			Responder [d]		
Mild	1/4 (25%)	3/4 (75%)	Mild	2/4 (50%)	3/4 (75%)
Moderate	7/8 (88%)	7/8 (88%)	Moderate	6/8 (75%)	7/8 (88%)
($CaCO_3$ 1 gm BID)			($CaCO_3$ 1 gm BID)		
Normalized [a]			Normalized [c]		
Mild	3/7 (43%)	5/7 (71%)	Mild	3/7 (43%)	5/7 (71%)
Moderate	0/6 (0%)	1/6 (17%)	Moderate	0/6 (0%)	1/6 (17%)
Responder [b]			Responder [d]		
Mild	1/7 (14%)	4/7 (57%)	Mild	5/7 (71%)	5/7 (71%)
Moderate	0/6 (0%)	2/6 (33%)	Moderate	1/6 (17%)	2/6 (33%)

a= OSBP<140 and DBP<90 mm Hg after treatment

b= OSBP or ODBP reduction of $\geq$ 10% from baseline after treatment

c= 24-hour SBP $\leq$ 130 and 24-hour DBP $\leq$ 80 mm Hg after treatment

d= 24-hour SBP or 24-hour DBP reduction of $\geq$ 10% from baseline after treatment

the add on effect after the second drug had been given in the treatments, some increments in the percentage of responders were found from either regimen.

When patients were classified as dippers/non-dippers according to nocturnal reduction of baseline MAP, in non-dipper group, the percentage of normalized patients based on their 24-hour ABP after treatment with HCTZ and $CaCO_3$ alone were 30% and 22% while dipper group were 100% and 25%, respectively. After the second drug has been given in each regimen, the increment of the percentage of normalized were found in either group except in non-dipper group who took HCTZ 25 mg OD for the single drug and $CaCO_3$ was used as the second drug for 4 weeks (Table 27).

When patients were categorized as responder and non-responder groups, the percentage of responded patients after treatment with HCTZ and $CaCO_3$ alone in non-dipper group were 60% and 56% while in dipper group were 100% and 25%. Considering on the effect of treatments, it was found that, the percentage of responders of the drug seem to be higher when the second drug has been given.

Part of the explanation might possibly due to the patients were more familiar and relax with the monitor machine while using the latter regimen and thus showed better antihypertensive response. This finding that the office SBP/DBP decreased by 17/11 mm Hg with HCTZ is similar to those reported in previous study by Materson BJ et al[72] and Neaton JD et al[73] which suggested that HCTZ could lower SBP by 15 to 20 mm Hg and DBP by 8 to 15 mm Hg while another previous investigations, Uzu T et al, found that after treatment with HCTZ 25 mg SBP/DBP reduced by 10/8 mm Hg[50]. With $CaCO_3$ 1 gm BID (elemental calcium 800 mg/d), the

Table 27: The effects of treatment on the numbers and the percentage of normalized and responded subjects based on office and 24-hour ambulatory blood pressure when the patients were classified as dippers/non-dippers according to nocturnal reduction of MAP

	Office blood pressure (OBP)			24-Ambulatory blood pressure (24-ABP)	
	Single drug	Combination drugs		Single drug	Combination drugs
(HCTZ 25 mg OD)			(HCTZ 25 mg OD)		
Normalized [a]			Normalized [c]		
Non-dipper	4/10 (40%)	3/10 (30%)	Non-dipper	3/10 (30%)	2/10 (20%)
Dipper	1/2 (50%)	1/2 (50%)	Dipper	2/2 (100%)	2/2 (100%)
Responder [b]			Responder [d]		
Non-dipper	6/10 (60%)	8/10 (80%)	Non-dipper	6/10 (60%)	8/10 (80%)
Dipper	2/2 (100%)	2/2 (100%)	Dipper	2/2 (100%)	2/2 (100%)
($CaCO_3$ 1 gm BID)			($CaCO_3$ 1 gm BID)		
Normalized [a]			Normalized [c]		
Non-dipper	1/9 (11%)	4/9 (44%)	Non-dipper	2/9 (22%)	4/9 (44%)
Dipper	2/4 (50%)	2/4 (50%)	Dipper	1/4 (25%)	2/4 (50%)
Responder [b]			Responder [d]		
Non-dipper	0/9 (0%)	3/9 (33%)	Non-dipper	5/9 (56%)	4/9 (44%)
Dipper	1/4 (25%)	3 /4 (75%)	Dipper	1/4 (25%)	3/4 (75%)

a= OSBP<140 and DBP<90 mm Hg after treatment

b= OSBP or ODBP reduction of $\geq$ 10% from baseline after treatment

c= 24-hour SBP $\leq$ 130 and 24-hour DBP $\leq$ 80 mm Hg after treatment

d= 24-hour SBP or 24-hour DBP reduction of $\geq$ 10% from baseline after treatment

result from this study indicated that office SBP/DBP was reduced by 1 / 2 mm Hg which was consistent with a previous study which found that calcium supplement could reduced SBP/DBP by 0.89 / 0.18 mm Hg[53] and also support by Cappuccio et al who found that women who took calcium supplement could have their SBP/DBP reduced by 0.150 / 0.057 mm Hg/ 100 mg calcium while in men, their SBP/DBP could only be reduced by 0.010 / 0.009 mm Hg/100 mg calcium[52].

4.3 Therapeutic effects of HCTZ and $CaCO_3$ on nocturnal reduction

When all patients were considered after treatment with HCTZ 25 mg OD plus $CaCO_3$ 1 gm BID, the percentage of nocturnal reduction of SBP and MAP were slightly increased from baseline ($p>0.31$), however, only the percentage of nocturnal reduction of DBP in group 1 were significantly increased from baseline ($p<0.01$) (Table 28).

When patients were classified to be mild or moderate hypertensive patients according to their office BP, moderate hypertensive patients had their percentage of nocturnal reduction increased from baseline to a greater extent as compared to the mild hypentensive patients (Table 29). From Table 30-31, HCTZ seem to cause increasing in percentage of nocturnal reduction of SBP, DBP and MAP more apparent in moderate hypertensive patients as compared to mild hypertensive patients whether it was used alone or combined drug with $CaCO_3$. The mean percentage of nocturnal reduction in mild hypertensive patients even showed decreasing when HCTZ was treatment alone.

In contrary, $CaCO_3$ 1 gm twice daily when used alone, besides small increasing in the percentage of nocturnal reductions of SBP in mild hypertensive patients and of DBP in

Table 28: Percentage of nocturnal decline in BP and number (percentage) of subjects who were dippers/non-dippers when classified by SBP, DBP and MAP at baseline and after treatment with hydrochlorothiazide or $CaCO_3$ alone when used the two drugs in combination

Parameters		Baseline (n=25)	HCTZ + $CaCO_3$ (n=25)[a]	Group 1 (n=12)			Group 2 (n=13)		
				Baseline	HCTZ [a]	HCTZ + $CaCO_3$ [a,b]	Baseline	$CaCO_3$ [a]	$CaCO_3$ + HCTZ [a,b]
Percentage of nocturnal decline									
SBP	(mean ± SD)	5.31 ± 6.74	6.34 ± 6.83^{+}	4.65 ± 6.98	6.19 ± 7.46^{+}	5.63 ± 8.46$^{+,+}$	5.92 ± 6.73	5.77 ± 6.10^{+}	7.00 ± 5.17$^{+,+}$
DBP	(mean ± SD)	7.54 ± 10.25	11.46 ± 8.73^{++++}	6.61 ± 6.81	8.98 ± 10.27^{+}	13.90 ± 10.39$^{*,++++}$	8.40 ± 12.88	7.06 ± 11.79^{+}	9.21 ± 6.50$^{+,+}$
MAP	(mean ± SD)	6.66 ± 7.19	9.31 ± 5.13^{++++}	5.81 ± 4.77	7.87 ± 7.79^{+}	10.33 ± 6.06$^{*,++}$	7.44 ± 9.00	6.39 ± 8.06^{+}	8.37 ± 4.13$^{+,+}$
Number (percentage) of dippers									
By SBP									
Non-dippers		17 (68)	16 (64)	9 (75)	8 (67)	6 (50)	8 (62)	11 (85)	10 (77)
Dippers		8 (32)	9 (36)	3 (25)	4 (33)	6 (50)	5 (38)	2 (15)	3 (23)
By DBP									
Non-dippers		17 (68)	10 (40)	9 (75)	6 (50)	4 (33)	8 (62)	9 (69)	6 (46)
Dippers		8 (32)	15 (60)	3 (25)	6 (50)	8 (67)	5 (38)	4 (31)	7 (54)
By MAP									
Non-dippers		19 (76)	12 (48)	10 (83)	6 (50)	4 (33)	9 (69)	8 (62)	8 (62)
Dippers		6 (24)	13 (52)	2 (17)	6 (50)	8 (67)	4 (31)	5 (38)	5 (38)

a compared to baseline of each group, b compared to before combination of the second drug

*** p<0.001, ** p<0.01, *p<0.05, ++++ p=0.05-0.10, +++ p=0.11-0.20, ++ p=0.21-0.30, + p>0.31

Table 29: Percentage of nocturnal reduction of BP at baseline and after treatment with HCTZ 25 mg OD combined with $CaCO_3$ 1 gm BID compared between mild and moderate hypertensive patients (classified according with their office SBP/DBP at baseline)

	Percentage of nocturnal reduction (n=25)	
	Baseline	**HCTZ + $CaCO_3$ / $CaCO_3$ + HCTZ**
SBP [c] (mean ± SD)		
mild (n=11)	8.30 ± 5.25	7.75 ± 6.86^{+}
moderate (n=14)	2.97 ± 7.01	5.24 ± 6.85^{++}
DBP [d] (mean ± SD)		
mild (n=11)	10.87 ± 11.98	11.40 ± 6.25^{+}
moderate (n=14)	4.94 ± 8.18	11.51 ± 10.52^{++++}
MAP [e] (mean ± SD)		
mild (n=11)	9.85 ± 7.92	10.09 ± 2.76^{+}
moderate (n=14)	4.14 ± 5.64	8.69 ± 6.47^{++++}

c,d,e = nocturnal reduction of SBP, DBP and MAP, respectively (%)

*** p<0.001, ** p<0.01, *p<0.05, ++++ p=0.05-0.10, +++ p=0.11-0.20, ++ p=0.21-0.30, + p>0.31

moderate hypertensive patients, the other type of BP showed decreasing in percentage of nocturnal reductions. When $CaCO_3$ was used as a second drug combined to HCTZ, the percentage of nocturnal reductions of nearly all types of BP of both mild and moderate hypertensive patients were increased except for the SBP of moderate hypertensive patients. Therefore, if dipper is considered as an advantage, consuming $CaCO_3$ as a nutritional supplement may cause some unfavorable effect while $CaCO_3$ was taken in combination with HCTZ, this unfavorable effect may be dissolved, causing the mean percentage of nocturnal reduction of most type of BP to be increased. However, these increasing and decreasing in the mean percentage of nocturnal reduction were mostly not statistically significant which could due in part to high variation among patients while the number of patients categorized into each group was small. Therefore, further studies in a large numbers of patients should be perform before any strong conclusion could be made.

When patients were classified as dippers/non-dipper according to nocturnal reduction of **baseline MAP**, six patients were classified dippers and nineteen patients were non-dippers (Table 28). The percentage of nocturnal reduction of BP at baseline and after treatment with HCTZ and $CaCO_3$ alone and when used the two drugs in combination were shown in Table 32-33. (The percentage of nocturnal reduction of BP when the patients were classified as dippers/non-dippers according to nocturnal reduction of baseline SBP and DBP were demonstrated in Appendix S-T.)

Group 1 patients, after treatment with HCTZ 25 mg OD, nocturnal reduction of SBP was significantly increased from 13.53 ± 4.60 to17.24 ± 4.99 % in dipper group ($p<0.05$). In

Table 30: Percentage of nocturnal reduction of BP at baseline and after treatment with HCTZ and $CaCO_3$ alone and when used the two drugs in combination (compared between mild and moderate hypertensive patients)

	Percentage of nocturnal reduction of BP					
	Group 1 (n=9)			Group 2 (n=10)		
	Baseline	HCTZ[a]	HCTZ + $CaCO_3$ [a,b]	Baseline	$CaCO_3$ [a]	$CaCO_3$ + HCTZ[a,b]
SBP [c] (mean ± SD)				**SBP** [c] (mean ± SD)		
mild (n=2)	10.87 ± 5.08	9.33 ± 8.78^{+}	9.90 ± 7.70$^{+,+}$	mild (n=6)	6.83 ± 5.10	8.31 ± 6.67^{+}	6.51 ± 6.63$^{+,+}$
moderate (n=7)	1.55 ± 5.69	4.63 ± 6.78^{+}	3.49 ± 8.45$^{+,+}$	moderate (n=4)	4.87 ± 8.66	2.80 ± 4.06^{+}	7.58 ± 3.26$^{+,*}$
DBP [d] (mean ± SD)				**DBP** [d] (mean ± SD)		
mild (n=2)	7.65 ± 3.41	3.10 ± 7.93^{+}	11.80 ± 8.81$^{++,++}$	mild (n=6)	12.71 ± 14.92	8.99 ± 10.39^{+}	11.17 ± 5.11$^{+,+}$
moderate (n=7)	6.11 ± 8.19	11.91 ± 10.45^{++}	14.95 ± 11.51$^{++++,+}$	moderate (n=4)	3.38 ± 8.67	4.82 ± 13.89^{+}	6.92 ± 7.63$^{+,+}$
MAP [e] (mean ± SD)				**MAP** [c] (mean ± SD)		
mild (n=2)	8.98 ± 1.04	5.98 ± 7.30^{+}	11.15 ± 2.28$^{+++,++}$	mild (n=6)	10.34 ± 10.16	8.70 ± 8.17^{+}	9.49 ± 2.99$^{+,+}$
moderate (n=7)	4.21 ± 5.16	8.81 ± 8.34^{++}	9.91 ± 7.40$^{++++,+}$	moderate (n=4)	4.05 ± 6.75	3.70 ± 7.72^{+}	7.07 ± 5.14$^{+,++}$

a compared to baseline of each group, b compared to before combination of the second drug

c,d,e = nocturnal reduction of SBP, DBP and MAP, respectively (%)

*** p<0.001, ** p<0.01, *p<0.05, ++++ p=0.05-0.10, +++ p=0.11-0.20, ++ p=0.21-0.30, + p>0.31

Table 31: Comparison of percentage of nocturnal reduction of BP after treatment with HCTZ or $CaCO_3$ alone as compared to baseline and after combination of the two drugs as compared to one drug (compared between mild and moderate hypertensive patients)

	Comparison of percentage of nocturnal reduction of BP					
	Group 1 (n=12)			Group 2 (n=13)		
	HCTZ vs baseline (1)[a]	HCTZ + $CaCO_3$ vs baseline (2)[a]	(2)-(1)[b]	$CaCO_3$ vs baseline (3)[a]	$CaCO_3$ + HCTZ vs baseline (4)[a]	(4)-(3)[b]
SBP [c]						
mild (n=4)	$\downarrow 2^{+}$	$\downarrow 1^{+}$	$\uparrow 1^{+}$	mild (n=7)	$\uparrow 2^{+}$	$\leftrightarrow^{+}$	$\downarrow 2^{+}$
moderate (n=8)	$\uparrow 3^{+}$	$\uparrow 2^{+}$	$\downarrow 1^{+}$	moderate (n=6)	$\downarrow 2^{+}$	$\uparrow 3^{+}$	$\uparrow 5^{*}$
DBP [d]						
mild (n=4)	$\downarrow 5^{+}$	$\uparrow 4^{++}$	$\uparrow 9^{++}$	mild (n=7)	$\downarrow 4^{+}$	$\downarrow 1^{+}$	$\uparrow 3^{+}$
moderate (n=8)	$\uparrow 6^{++}$	$\uparrow 9^{++++}$	$\uparrow 3^{+}$	moderate (n=6)	$\uparrow 2^{+}$	$\uparrow 4^{+}$	$\uparrow 2^{+}$
MAP [e]						
mild (n=4)	$\downarrow 3^{+}$	$\uparrow 2^{+++}$	$\uparrow 5^{++}$	mild (n=7)	$\downarrow 2^{+}$	$\downarrow 1^{+}$	$\uparrow 1^{+}$
moderate (n=8)	$\uparrow 5^{++}$	$\uparrow 6^{++++}$	$\uparrow 1^{+}$	moderate (n=6)	$\leftrightarrow^{+}$	$\uparrow 3^{+}$	$\uparrow 3^{++}$

a compared to baseline of each group, b compared to before combination of the second drug

c,d,e = nocturnal reduction of SBP, DBP and MAP, respectively (%)

*** $p<0.001$, ** $p<0.01$, *$p<0.05$, ++++ $p=0.05$-0.10, +++ $p=0.11$-0.20, ++ $p=0.21$-0.30, + $p>0.31$

the non-dipper group, nocturnal reductions of SBP, DBP and MAP were all increased but not to the extent that were considered as statistically significant ($p>0.31$). After $CaCO_3$ 1 gm BID had been combined, in non-dipper group, there was a significant increasing of nocturnal MAP reduction from 4.48 ± 3.90 to 9.98 ± 6.55 % ($p<0.05$) and six out of ten patients who were non-dippers had their BP patterns shifted to dippers.

Group 2 patients, the non-dippers who received $CaCO_3$ 1 gm BID for 4 weeks, the nocturnal reduction of SBP, DBP and MAP were all increased but not statistically significant ($p>0.31$). While for dippers, the nocturnal reduction of SBP, DBP and MAP were all decreased even though the decrement of MAP nocturnal reduction was statistically significant ($p<0.05$). After HCTZ 25 mg OD had been combined, the non-dippers, showed significant increase in nocturnal DBP and MAP reduction ($p<0.01$, $p<0.05$) while for dippers, the nocturnal reduction of SBP and MAP were significantly decreased at $p <0.05$ therefore four out of nine patients who were non-dippers had their BP patterns shifted to dippers while three of the four patients who were dippers had their BP patterns changed to non-dippers.

HCTZ caused increasing in the percentage of nocturnal reduction of SBP, DBP and MAP in the non-dipper group no matter when it was used alone or added on to the $CaCO_3$ therapy. However, for dippers, the result were uncertain the percentage of nocturnal reduction in BP could either increase or decrease after HCTZ had been taken, no matter as the first or the second drug in the regimen.

Consuming $CaCO_3$ could increase in the percentage of nocturnal reduction of SBP, DBP and MAP of non-dippers whether it was used as the first or the second drug and can

Table 32: Percentage of nocturnal reduction of BP at baseline and after treatment with HCTZ and $CaCO_3$ alone and when used the two drugs in combination when the patients were classified as dippers/non-dippers according to nocturnal reduction of baseline MAP

	Percentage of nocturnal reduction of BP					
	Group 1 (n=12)			Group 2 (n=13)		
	Baseline	HCTZ[a]	HCTZ + $CaCO_3$[a,b]	Baseline	$CaCO_3$[a]	$CaCO_3$ + HCTZ[a,b]
SBP[c] (mean ± SD)				SBP[c] (mean ± SD)		
non-dippers (n=10)	2.87 ± 6.01	3.96 ± 5.71^{+}	4.10 ± 8.47$^{+,+}$	non-dippers (n=9)	3.10 ± 6.14	5.43 ± 6.51^{+}	8.33 ± 5.52$^{++++,+++}$
dippers (n=2)	13.53 ± 4.60	17.24 ± 4.99*	13.14 ± 1.44$^{+,+}$	dippers (n=4)	12.26 ± 1.80	6.55 ± 5.91^{+++}	4.04 ± 2.99$^{**,+}$
DBP[d] (mean ± SD)				DBP[d] (mean ± SD)		
non-dippers (n=10)	5.62 ± 6.38	9.35 ± 11.02^{+}	14.41 ± 11.10$^{++++,+++}$	non-dippers (n=9)	2.59 ± 7.07	7.00 ± 13.97^{++}	8.93 ± 6.32$^{*,+}$
dippers (n=2)	11.54 ± 9.24	7.07 ± 7.92^{+++}	11.29 ± 7.89$^{+,***}$	dippers (n=4)	21.47 ± 14.20	7.18 ± 6.04^{++++}	9.85 ± 7.83$^{++++,+}$
MAP[e] (mean ± SD)				MAP[e] (mean ± SD)		
non-dippers (n=10)	4.48 ± 3.90	6.98 ± 8.30^{+}	9.98 ± 6.55$^{*,++}$	non-dippers (n=9)	2.88 ± 4.46	6.22 ± 9.32^{++}	8.70 ± 4.56$^{**,+}$
dippers (n=2)	12.43 ± 2.82	12.35 ± 1.63^{+}	12.05 ± 2.90$^{+,+}$	dippers (n=4)	17.68 ± 8.30	6.79 ± 5.26*	7.69 ± 3.42$^{*,+}$

a compared to baseline of each group, b compared to before combination of the second drug

c,d,e = nocturnal reduction of SBP, DBP and MAP, respectively (%)

*** p<0.001, ** p<0.01, *p<0.05, ++++ p=0.05-0.10, +++ p=0.11-0.20, ++ p=0.21-0.30, + p>0.31

Table 33: Comparison of percentage of nocturnal reduction of BP at baseline and after treatment with HCTZ and $CaCO_3$ alone and when used the two drugs in combination when the patients were classified as dippers/non-dippers according to nocturnal reduction of baseline MAP

	Comparison of percentage of nocturnal reduction of BP					
	Group 1 (n=12)			Group 2 (n=13)		
	HCTZ vs baseline (1)[a]	HCTZ + $CaCO_3$ vs baseline (2)[a]	(2)-(1)[b]	$CaCO_3$ vs baseline (3)[a]	$CaCO_3$ + HCTZ vs baseline (4)[a]	(4)-(3)[b]
SBP[c]				**SBP**[c]		
non-dippers (n=10)	$\uparrow 1^{+}$	$\uparrow 2^{+}$	$\uparrow 1^{+}$	non-dippers (n=9)	$\uparrow 3^{+}$	$\uparrow 6^{++++}$	$\uparrow 3^{+++}$
dippers (n=2)	$\uparrow 3^{*}$	$\downarrow 1^{+}$	$\downarrow 4^{+}$	dippers (n=4)	$\downarrow 5^{+++}$	$\downarrow 8^{**}$	$\downarrow 3^{+}$
DBP[d]				**DBP**[d]		
non-dippers (n=10)	$\uparrow 4^{+}$	$\uparrow 9^{++++}$	$\uparrow 5^{+++}$	non-dippers (n=9)	$\uparrow 4^{++}$	$\uparrow 6^{*}$	$\uparrow 2^{+}$
dippers (n=2)	$\downarrow 5^{+++}$	$\leftrightarrow^{+}$	$\uparrow 5^{***}$	dippers (n=4)	$\downarrow 14^{++++}$	$\downarrow 11^{++++}$	$\uparrow 3^{+}$
MAP[e]				**MAP**[e]		
non-dippers (n=10)	$\uparrow 2^{+}$	$\uparrow 5^{*}$	$\uparrow 3^{++}$	non-dippers (n=9)	$\uparrow 3^{++}$	$\uparrow 6^{**}$	$\uparrow 3^{+}$
dippers (n=2)	$\leftrightarrow^{+}$	$\leftrightarrow^{+}$	$\leftrightarrow^{+}$	dippers (n=4)	$\downarrow 11^{*}$	$\downarrow 10^{*}$	$\uparrow 1^{+}$

a compared to baseline of each group, b compared to before combination of the second drug

f,g,h = nocturnal reduction of SBP, DBP and MAP, respectively (%)

*** p<0.001, ** p<0.01, *p<0.05, ++++ p=0.05-0.10, +++ p=0.11-0.20, ++ p=0.21-0.30, + p>0.31

cause the BP pattern of some patients to change from non-dippers to dippers which is considered as an advantage. However, for dippers, the result were opposite, most of the time when $CaCO_3$ had been consumed by dippers their percentage of nocturnal reduction were decreased especially when $CaCO_3$ was alone. This could cause the BP pattern of patients change form dipper to non-dipper which is considered as disadvantage.

In this study, the effects of HCTZ on blood pressure, frequency of blood pressure loads and the percentage of nocturnal reduction when used as the second drug combined with $CaCO_3$ seem to be less than when HCTZ was used as the first drug due to several reasons i.e., 1) The mean age of patients in group 2 was less than that of group 1, from the previous study suggested that HCTZ was less effective in younger patients.[72] 2) Doses of HCTZ per kg body weight of patients in group 2 were less than those of the patients in group 1. 3) Eight patients in group 2 used to take thiazide-diuretic to treat their hypertension, they may resistant to HCTZ.

While the effects of $CaCO_3$ on blood pressure, frequency of blood pressure loads and the percentage of nocturnal reduction were modest whether when the drug was used as the first drug or in combination with HCTZ because of many reason i.e. 1) In previous studies, elemental doses of calcium which could effectively reduced BP were 1000-1500mg per day[44,73-74], but in this study the patients had received only 800 mg per day. 2) Thirteen patients drank caffeine, two patients drank alcohol and two patients currently smoked cigarettes, these could suppress intestinal calcium absorption. 3) The failure to observed a consistent effect could be the result of impaired intestinal absorption of calcium which may develop in the elderly. 4) Calcium

supplement may be required for woman especially elderly and pregnant than for men to reduced BP.[74-75]

4.4 The effect of HCTZ and $CaCO_3$ on 24-hour urinary excretion

All patients in this study had normal renal function since either Clcr values calculated by using 24-hour urine collection and those obtained from Cockcroft and Gault formula were all within normal range. After patients in group 1 had been treated with HCTZ 25 mg per day for 4 weeks, it was found that 24-hour urinary sodium excretion was increased from 134.53 $\pm$ 53.60 to 167.90 $\pm$ 83.41 mEq/24 hr and %FENa was increased from 0.94 $\pm$ 0.24 to 1.21 $\pm$ 0.36 % ($p=0.21$-0.30) because HCTZ inhibited reabsorption of sodium. At the same time, the 24-hour urinary calcium excretion and %FECal were reduced from 113.00 $\pm$ 100.35 to 106.49 $\pm$ 125.92 mg/24 hr and from 1.05 $\pm$ 0.62 to 1.01 $\pm$ 0.92 %, respectively ($p>0.31$). After $CaCO_3$ 1 gm BID had been added in place of placebo for another 4 weeks, %FENa was further increased and was higher than treatment with HCTZ alone ($p<0.05$).

On the other hand, patients who started their regimen by received $CaCO_3$ 1 gm BID plus placebo of HCTZ were found to have their 24-hour urinary sodium excretion and %FE Na reduced from 172.59 $\pm$ 92.19 to 162.44 $\pm$ 60.33 mEq/24hr and from 1.01 $\pm$ 0.49 to 1.00 $\pm$ 0.32 % ($p>0.31$). While 24-hour urinary calcium excretion and %FECal were significantly increased from 154.11 $\pm$ 59.20 to 200.72 $\pm$ 82.83 mEq/24hr and from 1.37 $\pm$ 0.60 to 1.75 $\pm$ 0.59 % ($p<0.05$). After HCTZ was added on as a combination therapy for another 4 weeks, 24-hour urinary sodium excretion and %FENa were dropped more than treatment with HCTZ alone but showed no statistically significant ($p>0.31$) (Table 34).

Table 34: Laboratory data 24-hour excretion of urine of the subjects at baseline and after treatment with hydrochlorothiazide or $CaCO_3$ alone and when used the two drugs in combination[1]

Test (normal range)	Baseline[2] (n=21)	HCTZ + $CaCO_3$[2] (n=21)[a]	Group 1 (n=9)[2]			Group 2 (n=12)[2]		
			Baseline	HCTZ[a]	HCTZ + $CaCO_3$[a,b]	Baseline	$CaCO_3$[a]	$CaCO_3$ + HCTZ[a,b]
Creatinine (1000-2000 mg/24 hr)	1053.38 ± 326.72	997.78 ± 252.57^{++}	968.39 ± 296.15	986.00 ± 296.88^{+}	921.60 ± 255.12$^{+,++}$	1117.12 ± 346.34	1087.94 ± 310.78^{++}	1054.92 ± 245.63$^{+,+}$
Sodium (40-220 mEq/24 hr)	156.28 ± 78.72	156.10 ± 73.94^{+}	134.53 ± 53.60	167.90 ± 83.41^{++}	167.31 ± 98.56$^{++,+}$	172.59 ± 92.19	162.44 ± 60.33^{+}	147.68 ± 51.93$^{+,+}$
Calcium (50-250 mg/24 hr)	136.49 ± 79.94	169.95 ± 95.74^{++++}	113.00 ± 100.35	106.49 ± 125.92^{+}	168.17 ± 134.32$^{++,++}$	154.11 ± 59.20	200.72 ± 82.83**	171.28 ± 59.48$^{++,++++}$
% FENa	0.98 ± 0.39	1.12 ± 0.46^{+++}	0.94 ± 0.24	1.21 ± 0.36^{+++}	1.31 ± 0.48$^{*,+}$	1.01 ± 0.49	1.00 ± 0.32^{+}	0.98 ± 0.40$^{+,+}$
% FECal	1.23 ± 0.61	1.68 ± 0.84*	1.05 ± 0.62	1.01 ± 0.92^{+}	1.76 ± 1.17$^{+++,+++}$	1.37 ± 0.60	1.75 ± 0.59*	1.62 ± 0.52$^{++++,++}$
Clcr (from laboratory) (ml/min)	78.58 ± 20.17	71.08 ± 21.46*	71.59 ± 23.22	66.95 ± 19.78^{++}	63.39 ± 27.23$^{+++,+}$	83.82 ± 16.66	81.81 ± 22.98^{+}	76.83 ± 14.61$^{++++,+}$
Clcr (from calculation) (ml/min)	62.27 ± 17.97	60.11 ± 21.62^{+}	55.38 ± 20.38	51.03 ± 18.22^{++++}	50.66 ± 22.02$^{*,+}$	67.44 ± 14.74	66.99 ± 18.96^{+}	67.20 ± 19.21$^{+,+}$

1 After excluded 4 patients

2 data are shown as mean ± SD

a versus baseline of each group; b versus before combined second drugs

*** p<0.001, ** p<0.01, *p<0.05, ++++ p=0.05-0.10, +++ p=0.11-0.20, ++ p=0.21-0.30, + p>0.31

When patients who were classified as mild or moderate hypertension groups, the values of 24-hour urinary sodium, calcium excretion, %FENa and %FECal of mild hypertensive patients were lower than those of moderate hypertensive patients (Table 35). In mild and moderate hypertensive patients, after treatment with HCTZ alone for 4 weeks 24-hour urinary sodium excretion and %FENa were increased at $p>0.31$. After $CaCO_3$ 1 gm BID had been combined for another 4 weeks, 24-hour urinary sodium excretion and %FENa in mild hypertensive patients were reduced. In contrary, for patients who were moderate hypertensive, the excretion of sodium in urine was increasing from baseline and from after treatment with HCTZ alone. 24-hour excretion of calcium and % FECal were both increased from baseline either group of patients after $CaCO_3$ was used to add on the HCTZ therapy as expected since more calcium had been consumed.

At the same time, patients (group 2) who took $CaCO_3$ 1 gm BID as their starting regimen showed their 24-hour urinary sodium excretion and % FENa to be decreased from baseline and after combination with HCTZ 25 mg in either mild or moderate hypertensive patients ($p>0.31$). Patients excreted higher amount of calcium in urine after they received $CaCO_3$ 1 gm BID, however, after HCTZ had been combined for 4 more weeks, the 24-hour urinary calcium excretion was dropped but showed no statistically significant ($p>0.31$).

Patients were classified as dippers and non-dippers based on their nocturnal BP reduction either from baseline SBP, DBP or MAP. Four patients were excluded due to their total creatinine in the 24-hour urine specimen fell below the normal range. When the classification was based on the nocturnal reduction of baseline DBP and MAP, there was only one patient who was

Table 35: Laboratory data 24-hour excretion of urine of the mild/moderate hypertensive subjects at baseline and after treatment with hydrochlorothiazide or $CaCO_3$ alone and when used the two drugs in combination

Test (normal range)	Mild/Moderate hypertension based on office SBP/DBP at baseline							
	Baseline[2]	HCTZ + $CaCO_3$[2,1]	Group 1[2]			Group 2[2]		
			Baseline	HCTZ[a]	HCTZ + $CaCO_3$[a,b]	Baseline	$CaCO_3$[a]	$CaCO_3$ + HCTZ[a,b]
Mild hypertension	(n=9)	(n=9)	(n=3)	(n=3)	(n=3)	(n=6)	(n=6)	(n=6)
Creatinine (1000-2000 mg/24 hr)	1059.22 ± 256.15	1053.89 ± 218.26^{+}	1209.33 ± 287.19	1246.40 ± 273.94^{+}	1147.40 ± 247.15$^{+,++++}$	984.17 ± 227.40	974.77 ± 217.78^{+}	1007.13 ± 209.57$^{+,+}$
Sodium (40-220 mEq/24 hr)	145.56 ± 36.65	142.87 ± 60.83^{+}	147.80 ± 65.95	216.27 ± 54.84^{+}	157.37 ± 75.35$^{+,+}$	144.43 ± 20.12	144.07 ± 41.61^{+}	135.62 ± 58.83$^{+,+}$
Calcium (50-250 mg/24 hr)	123.44 ± 59.98	176.07 ± 93.29^{+++}	97.20 ± 63.87	109.80 ± 39.20^{+}	215.67 ± 145.86$^{+,+}$	136.57 ± 59.21	172.48 ± 63.88^{+++}	156.27 ± 63.27$^{+,+}$
% FENa	0.91 ± 0.19	1.05 ± 0.52^{+}	0.99 ± 0.32	1.50 ± 0.36^{+}	1.31 ± 0.74$^{+,+}$	0.86 ± 0.08	0.83 ± 0.11^{+}	0.92 ± 0.39$^{+,+}$
% FECal	1.11 ± 0.44	1.83 ± 1.00^{++++}	0.99 ± 0.62	1.12 ± 0.48^{+}	2.44 ± 1.59$^{++,+}$	1.17 ± 0.38	1.41 ± 0.29^{++}	1.52 ± 0.51$^{+++,+}$
Clcr (from laboratory) (ml/min)	79.17 ± 14.00	69.48 ± 9.78*	72.12 ± 9.62	71.56 ± 6.08^{+}	62.54 ± 6.41$^{+,+}$	82.70 ± 15.23	85.84 ± 26.91^{+}	72.96 ± 9.66$^{+++,++}$
Clcr (from calculation) (ml/min)	64.42 ± 14.11	57.35 ± 15.19*	56.53 ± 8.78	54.49 ± 7.73^{+}	51.68 ± 8.42$^{+,+}$	68.36 ± 15.23	71.21 ± 23.02^{+}	60.19 ± 17.66$^{*,+++}$
Moderate hypertension	(n=12)	(n=12)	(n=6)	(n=6)	(n=6)	(n=6)	(n=6)	(n=6)
Creatinine (1000-2000 mg/24 hr)	1048.99 ± 382.51	1004.28 ± 299.44^{+}	847.92 ± 234.70	855.80 ± 223.56^{+}	866.20 ± 284.89$^{+,+}$	1250.07 ± 412.03	1226.25 ± 370.56^{+}	1142.37 ± 265.23$^{++,+}$
Sodium (40-220 mEq/24 hr)	164.32 ± 100.62	175.86 ± 90.25^{+}	127.89 ± 51.94	143.72 ± 88.45^{+}	181.80 ± 116.61$^{++++,++}$	200.75 ± 128.02	184.33 ± 73.61^{+}	169.92 ± 65.10$^{+,+}$
Calcium (50-250 mg/24 hr)	146.28 ± 93.59	171.47 ± 99.71^{++}	120.90 ± 119.39	104.83 ± 157.31^{+}	149.80 ± 133.63$^{+,+}$	171.65 ± 58.87	232.07 ± 92.47*	193.13 ± 53.77$^{+++,+++}$
% FENa	1.04 ± 0.49	1.18 ± 0.42^{+}	0.92 ± 0.22	1.06 ± 0.27^{++}	1.32 ± 0.39$^{++++,+++}$	1.17 ± 0.67	1.16 ± 0.38^{+}	1.05 ± 0.45$^{+,+}$
% FECal	1.32 ± 0.72	1.58 ± 0.71^{++}	1.08 ± 0.68	0.96 ± 1.12^{+}	1.43 ± 0.87$^{+,+}$	1.56 ± 0.74	2.08 ± 0.64**	1.73 ± 0.55$^{++,*}$
Clcr (from laboratory) (ml/min)	78.13 ± 24.43	74.97 ± 26.59^{+++}	71.32 ± 28.74	64.65 ± 24.33^{+++}	66.17 ± 32.78$^{++,+}$	84.94 ± 19.39	79.72 ± 22.04^{+}	83.77 ± 17.18$^{+,+}$
Clcr (from calculation) (ml/min)	60.67 ± 20.88	62.18 ± 25.90^{+}	54.81 ± 25.15	49.31 ± 22.29^{+++}	50.15 ± 27.32$^{++++,+}$	66.53 ± 15.62	62.77 ± 14.78^{+}	74.21 ± 19.55$^{++,**}$

1 After excluded 4 patients, 2 data are shown as mean ± SD

a compared to baseline of each group, b compared to before combination of the second drug

*** p<0.001, ** p<0.01, *p<0.05, ++++ p=0.05-0.10, +++ p=0.11-0.20, ++ p=0.21-0.30, + p>0.31

categorized as dipper in group 1 as demonstrated in detail in appendix U and V. The number of subjects in this category was therefore too small for any further discussion in the statistically point of view. Therefore, the classification as dippers/non-dippers based on the nocturnal reduction of baseline SBP was used to calculated data in Table 36.

In patients who were classified as non-dippers, their 24-hour sodium excretion and %FENa were lower than the dippers at baseline. In contrary, non-dippers excreted higher amount of calcium in urine at baseline.

In non-dippers group, patients who took HCTZ or $CaCO_3$ alone, their 24-hour urinary sodium excretion and %FENa were increased from baseline but not statistically significant ($p>0.31$). Patients whose treatment was HCTZ alone the excretion of calcium were decreased ($p>0.31$). After $CaCO_3$ 1 gm BID had been combined with HCTZ in patients group 1, the 24-hour urinary sodium excretion and %FENa were increased ($p>0.31$), while patients in group 2 after HCTZ had been combined were small further change in 24-hour sodium excretion was observed.

While patients who were classified as dippers, their 24-hour excretion of sodium was increased after treatment with HCTZ but these values was dropped after combined with $CaCO_3$ ($p>0.31$). In patients (group 2) who had received $CaCO_3$ 1 gm BID alone, the excretion of sodium in urine was lowered from baseline but showed no statistically significant ($p>0.31$). At the same time, the 24-hour excretion of calcium was increased from baseline after treatment with $CaCO_3$ alone and this increment was reduced after HCTZ had been combined (Table 36).

Table 36: Laboratory data 24-hour excretion of urine of the dippers/non-dippers subjects at baseline and after treatment with hydrochlorothiazide or $CaCO_3$ alone and when used the two drugs in combination[1]

Test (normal range)	Dippers/Non-dippers based on nocturnal reduction of baseline SBP							
	Baseline	HCTZ + $CaCO_3$[a]	Group 1			Group 2		
			Baseline	HCTZ[a]	HCTZ + $CaCO_3$[a,b]	Baseline	$CaCO_3$[a]	$CaCO_3$ + HCTZ[a,b]
Non-dippers (mean ± SD)	(n=14)	(n=14)	(n=7)	(n=7)	(n=7)	(n=7)	(n=7)	(n=7)
Creatinine (1000-2000 mg/24 hr)	976.28 ± 340.50	964.11 ± 268.29^{+}	862.50 ± 217.70	866.54 ± 206.05^{+}	867.20 ± 260.08$^{+,+}$	1090.06 ± 416.66	1094.90 ± 376.68^{+}	1061.03 ± 257.68$^{+,+}$
Sodium (40-220 mEq/24 hr)	143.03 ± 47.84	165.32 ± 79.64^{++}	130.69 ± 47.99	150.33 ± 82.62^{++}	166.61 ± 113.78$^{+,+}$	155.36 ± 47.96	164.73 ± 39.54^{+}	164.03 ± 28.15$^{+,+}$
Calcium (50-250 mg/24 hr)	147.25 ± 88.18	169.08 ± 96.68^{++}	127.91 ± 110.56	111.30 ± 144.62^{+}	147.86 ± 122.09$^{+,+}$	166.59 ± 61.25	208.44 ± 101.87^{++++}	190.30 ± 65.52$^{*,+}$
% FENa	0.93 ± 0.18	1.14 ± 0.36^{++++}	0.93 ± 0.20	1.12 ± 0.29^{+++}	1.21 ± 0.46$^{+++,+}$	0.93 ± 0.18	1.01 ± 0.28^{+}	1.07 ± 0.24$^{+++,+}$
% FECal	1.34 ± 0.67	1.59 ± 0.68^{+++}	1.16 ± 0.66	1.06 ± 1.06^{+}	1.43 ± 0.79$^{+,+}$	1.51 ± 0.68	1.78 ± 0.75^{++++}	1.75 ± 0.56$^{++++,+}$
Clcr (from laboratory) (ml/min)	77.11 ± 23.50	72.06 ± 24.19^{+++}	71.61 ± 26.24	64.65 ± 22.21^{++++}	66.34 ± 29.93$^{+++,+}$	82.61 ± 20.92	84.93 ± 30.78^{+}	77.78 ± 17.21$^{+,+}$
Clcr (from calculation) (ml/min)	61.26 ± 20.24	58.42 ± 24.51^{+}	55.75 ± 23.09	50.15 ± 20.47^{++++}	51.75 ± 25.30$^{++++,+}$	66.78 ± 16.83	67.69 ± 25.03^{+}	65.09 ± 23.60$^{+,+}$
Dippers (mean ± SD)	(n=7)	(n=7)	(n=2)	(n=2)	(n=2)	(n=5)	(n=5)	(n=5)
Creatinine (1000-2000 mg/24 hr)	1207.57 ± 250.99	1148.40 ± 218.28^{++}	1339.00 ± 253.14	1404.10 ± 29.58^{+}	1284.50 ± 96.87$^{+,++}$	1155 ± 257.65	1108.36 ± 255.72^{++}	1093.96 ± 236.97$^{+,+}$
Sodium (40-220 mEq/24 hr)	182.78 ± 120.27	154.51 ± 83.47^{+}	147.95 ± 93.27	229.40 ± 70.57^{+}	198.30 ± 36.06$^{+,+}$	196.72 ± 136.65	163.46 ± 88.36^{+}	137.00 ± 93.72$^{+++,+}$
Calcium (50-250 mg/24 hr)	114.96 ± 60.34	182.16 ± 97.29^{+++}	60.80 ± 14.42	89.65 ± 25.24^{+}	255.40 ± 181.87$^{+,+}$	136.63 ± 57.93	193.64 ± 52.22^{++++}	152.86 ± 46.65$^{+,++++}$
% FENa	1.10 ± 0.65	1.09 ± 0.65^{+}	0.99 ± 0.45	1.52 ± 0.50^{+}	1.69 ± 0.49$^{*,+}$	1.14 ± 0.75	0.98 ± 0.39^{+}	0.86 ± 0.57$^{+,+}$
% FECal	1.02 ± 0.45	1.87 ± 1.12^{+++}	0.66 ± 0.32	0.85 ± 0.18^{+}	2.93 ± 1.90$^{++,+}$	1.16 ± 0.44	1.70 ± 0.33^{++++}	1.44 ± 0.43$^{+,++++}$
Clcr (from laboratory) (ml/min)	81.51 ± 12.02	73.72 ± 13.39^{++++}	71.53 ± 13.53	75.01 ± 1.57^{+}	60.12 ± 6.85$^{+,++}$	85.51 ± 10.06	79.78 ± 10.00^{+}	79.17 ± 11.29$^{*,+}$
Clcr (from calculation) (ml/min)	64.30 ± 13.49	63.48 ± 15.39^{+}	54.10± 10.89	54.10 ± 10.89^{+}	46.83 ± 0.61$^{+,+}$	68.38 ± 13.05	65.99 ± 6.84^{+}	7 0.14 ± 12.68$^{+,+}$

1 After excluded 4 patients

a compared to baseline of each group, b compared to before combination of the second drug

*** p<0.001, ** p<0.01, *p<0.05, ++++ p=0.06-0.10, +++ p=0.11-0.20, ++ p=0.21-0.30, + p>0.31

CHAPTER V

CONCLUSION

1. Hydrochlorothiazide 25 mg administered once daily as a single drug could effectively reduce blood pressures. The percentage of normalized and responder subjects after treatment with HCTZ alone were 42% and 67%, respectively. DBP was slightly higher reduced than SBP. The extents of blood pressure reduction were nearly the same during day-time and night-time. Reduction in frequency of BP loads (%) were found in all types of BP either day-time or night-time. During day-time, the frequency of DBP loads was higher reduced than the frequency of SBP loads while the results were opposite when considered the effect during night-time.

   $CaCO_3$ when used as a combined drug with HCTZ, no further decrement in BP could be found for both SBP and DBP, however, the increment of the reduction in frequency of SBP loads were found during day-time. While DBP was slightly further reduced and increment of frequency of DBP loads reduction during night-time was observed. The percentage of responder was increased from 67% to 83%. However, HR was slightly reduced between baseline and after the second drug had been given.

2. Calcium carbonate 1 gm twice daily when used alone could slightly decrease blood pressures. The percentage of normalized and responder subjects after treatment with $CaCO_3$ alone were 23% and 46%, respectively. DBP was higher reduced than SBP and it seem to cause more reduction during day-time than during night-time. Frequency of SBP and DBP

loads was slightly decreased from baseline during day-time, however, the highest reduction in frequency of BP loads was found for DBP at night-time.

When HCTZ was combined to $CaCO_3$ slightly increment in BP and frequency of BP loads reduction were observed, thus, causing some BP and frequency of BP loads reduction from baseline to become statistically significant. The extent of BP reduction and frequency of BP loads reduction, however, were much less than when HCTZ was used as the first drug. The percentage of normalized and responder were increased to 46% and 54%, respectively.

3. When the patients were classified as mild and moderate hypertensive patients, treatment with HCTZ 25 mg OD alone could cause effective BP and frequency of BP loads reductions in both mild and moderate hypertensive patients, however, treatment effects were more apparent in the moderate hypertensive group.

In mild hypertensive group, the reduction in DBP and the frequency of DBP loads were more distinct than those reductions in SBP, day-time BP reduction was shown to be a little bit higher than night-time BP reduction. HCTZ was able to decrease BP of some mild hypertensive patients down to normal range (25%) and the percentage of responder was 50% when HCTZ was used as the first drug. $CaCO_3$ when added to combine therapy with HCTZ, increment reduction in BP and frequency of BP loads were found more obviously in SBP than DBP. Combination of the two drugs increased the antihypertensive effects of one drug. Therefore, the percentage of normalized and responder were increased to 50% and 75%, respectively.

In moderate hypertensive group, SBP and DBP were reduced to the same extent, with night-time BP reduction slightly more apparent than day-time BP reduction. The reduction in frequency of DBP loads during day-time were higher than frequency of DBP loads during night-time. The percentage of normalized and responder subjects after treatment with HCTZ alone were 50% and 75%, respectively. After $CaCO_3$ had been combined, no further reduction of BP and frequency of BP loads were found, the SBP and frequency of SBP loads were even increased. The percentage of responder was increased from 75% to 88%.

Treatment with $CaCO_3$ alone, both BP and frequency of BP loads were markedly reduced and the percentage of normalized and responder subjects after treatment with this regimen were 43% and 71%, respectively in mild hypertensive patients. While in moderate hypertensive patients, BP and frequency of BP loads not only not reduced but even became higher than baseline.

When HCTZ had been added to combine therapy with $CaCO_3$ small further BP reduction and frequency of BP loads reduction mostly the SBP, were found in the mild hypertensive group while no apparent increment in BP reduction and frequency of BP loads reduction could be found in the moderate hypertensive group. The regimen which HCTZ was used either as the first or the second drug could result in incretion of the percentage of normalized and responder especially in mild hypertensive patients.

4. When the patients were classified as dippers/non-dippers according to nocturnal reduction of baseline MAP, treatment with HCTZ, in non-dippers group, the reductions in DBP and

frequency of DBP loads were slightly higher than those of SBP, night-time BP reduction was shown to be a little bit higher than day-time BP reduction. The percentage of normalized and responder subjects after treatment with HCTZ were 30% and 60%, respectively. $CaCO_3$ when used as a combined drug with HCTZ, the increment of BP reduction and frequency of BP loads reduction were found more obviously in DBP than SBP during night-time. $CaCO_3$ did not further increase the effect of HCTZ, therefore the percentage of normalized did not increase from baseline, however, the percentage of responder were increased from 60% to 80%.

In dipper group, treatment with HCTZ alone, BP and frequency of BP loads were reduced more apparent than in non-dipper group, the extents of BP and frequency of BP loads reduction were nearly the same during day-time and night-time. After $CaCO_3$ had been combined with HCTZ, only further reduction in SBP and frequency of SBP loads during day-time were found. HCTZ could shift blood pressure of all dipper patients down to normal range whether when used alone or combined with $CaCO_3$.

Treatment with $CaCO_3$ alone, in dipper group, BP and frequency of BP loads were slightly decreased during day-time, while during night-time, BP and frequency of BP loads not only not reduced but even became higher than those at baseline. In non-dipper group, very slightly reduction in BP and frequency of BP loads were observed, however, DBP and frequency of DBP loads were higher reduced than SBP especially during night-time. $CaCO_3$ could decrease blood pressure of small percentage of both dippers and non-dippers to

normalized range, the percentage of normalized were nearly the same for dippers and non-dippers 25% and 22%, respectively.

When HCTZ was combined to $CaCO_3$, the increment of BP reduction and frequency of BP loads reduction were found only during night-time in the non-dipper group. In the dipper group further reductions as compared to $CaCO_3$ alone were found, however, the extent of BP reduction and frequency of BP loads reduction during night-time were much less than when HCTZ was used as the first drug. When used the combination drugs, the percentage of responder in either group seem to be higher when the second drug has been given.

5. HCTZ as a single drug could increase the percentage of nocturnal decline in BP especially DBP, while $CaCO_3$ alone, could not increase the percentage of nocturnal decline in BP and became less declined than at baseline in some patients. After $CaCO_3$ was combined with HCTZ, the increment of the percentage of nocturnal decline in DBP became statistically significant different from baseline while the percentage of nocturnal decline was slightly further increased after HCTZ was used as the second drug combined to $CaCO_3$.

HCTZ used as a single drug could change the BP pattern of some non-dipper patients to become dipper and this number was even increased after $CaCO_3$ was combined to HCTZ. In contrary, $CaCO_3$ when used alone might cause the BP pattern of some dipper patients to change to non-dipper but after HCTZ was added to combine with $CaCO_3$ the BP pattern of some patients was induced back to dipper.

6. 24-hour urinary sodium excretion and %FENa were increased after treatment with HCTZ alone while the 24-hour urinary calcium excretion and %FECal were decreased from baseline, no further increase in the amount of sodium excrete in urine after $CaCO_3$ was added on the therapy. In contrary, 24-hour urinary sodium excretion and %FENa were decreased from baseline after treatment with $CaCO_3$ alone or in combination with HCTZ.

7. The effects of calcium supplement and/or hydrochlorothiazide on 24-hour blood pressure in primary hypertension should be studies in larger sample sizes, especially in mild hypertensive patients and non-dipper group. It is very promising that calcium supplement may extend the efficiency of other antihypertensive drugs in most postmenopausal women.

Conclusion of the effects of HCTZ and $CaCO_3$ on blood pressure, frequency of BP loads and percentage of nocturnal reduction in BP

Treatment	Mild hypertension			Moderate hypertension			Non-dipper group			Dipper group		
	a	b	c	a	b	c	a	b	c	a	b	c
HCTZ alone	+	+ (n=4)	-	+	+ (n=8)	+	+	+ (n=10)	+	+	+ (n=2)	±
$CaCO_3$ alone	+	+ (n=7)	±	-	- (n=6)	±	+	± (n=9)	+	±	± (n=4)	-
$CaCO_3$ was added on to HCTZ	+	+ (n=4)	+	-	± (n=8)	+	+	+ (n=10)	+	±	± (n=2)	±
HCTZ was added on to $CaCO_3$	+	+ (n=7)	+	+	+ (n=6)	+	+	± (n=9)	+	+	+ (n=4)	±

a = effects on blood pressure

b = effects on frequency of blood pressure loads

c = effects on the percentage of nocturnal reduction in BP

+ = positive result

- = negative result

± = both positive and negative result

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APPENDICES

Appendix A: Demographic data of the individual subjects (n=25)

No.	Group	Sex	Age (years)	Weight (kg.)	Height (cm.)	BMI (kg/m2)	Life style	24- hour ABP at baseline			Duration of HT (years)
								SBP	DBP	MAP	
1	2	female	66	69.8	160	27.27	&	164	110	128	7
2	1	male	51	65.0	164	24.16	&	152	111	125	4
3	1	female	79	51.7	155	21.54	$	153	106	122	20
4	2	female	69	61.7	160	24.10	$, &	140	92	108	5
5	1	male	67	59.5	156	24.49	/	138	99	112	4
6	1	male	69	67.0	170	23.18	*, $	156	90	112	1
7	1	female	54	74.0	150	32.89	&	155	111	126	5
8	2	male	54	78.0	168	27.66	*, $	133	87	102	11
9	1	female	81	31.2	148	14.25	&	147	113	124	2
10	2	female	42	56.4	155.5	23.21	&	134	101	112	4
11	2	female	58	65.6	156	27.00	$, &	126	86	99	10
12	2	female	54	46.0	150	20.44	$	131	85	100	1
13	2	female	52	64.6	154	27.26	-	155	85	108	3
14	2	male	61	73.0	162	27.86	$	163	97	119	6
15	1	female	64	60.5	156	24.90	-	123	85	98	2
16	1	female	60	58.5	152	25.32	$	141	78	99	0
17	1	female	65	75.2	163	28.27	$	142	69	93	9
18	1	female	51	66.0	160	25.78	$	143	78	100	1
19	2	male	63	67.0	167	24.01	/	130	85	100	1
20	1	female	74	74.5	161	28.76	$	133	85	101	3
21	2	female	76	53.5	165	19.67	&	148	88	108	6
22	2	female	59	52.4	151	22.98	-	124	87	100	2
23	2	female	57	60.6	152	26.23	$, &	128	85	99	0
24	1	female	56	47.7	152	20.65	&	138	91	107	6
25	2	female	62	56.7	153.5	23.92	$	131	85	100	7

* Smoking

/ Drinking alcohol

$ Drinking caffeine

& Drinking milk

Appendix B: Laboratorydata of the individual subjects at baseline (n=25)

NO.	FBS (60-100 mg/dl)	TC (150-220mg/dl)	TG (40-155 mg/dl)	HDL (50-100 mg/dl)	LDL (130-159 mg/dl)	BUN (5-20 mg/dl)	Cr (0.5-1.2 mg/dl)	Na (135-150 mEq/l)	Cal (9-11 mg/dl)	K (3.5-5.0 mg/dl)	phosphate (2.5-4.8 mg/dl)	Alb (3.8-5.0 g/dl)	SGOT (0.38 U/l)	SGPT (0-38 U/l)	uric acid (2.0-7.0 mg/dl)
1	94	203	307	29	113	12	1.0	137.0	9.3	3.8	3.3	5.1	12.0	15.0	3.1
2	86	201	116	36	142	17	1.3	140.0	10.0	4.6	3.2	4.7	25.0	23.0	4.0
3	96	179	165	67	79	15	1.0	141.0	9.6	3.9	3.9	4.6	33.0	35.0	2.7
4	91	203	138	58	118	12	0.9	145.0	9.0	3.6	2.9	4.7	22.0	25.0	2.8
5	96	196	79	57	124	14	1.3	138.0	9.0	3.5	2.3	4.8	31.0	34.0	3.4
6	93	234	101	45	169	14	1.1	142.0	9.5	3.5	2.8	4.9	33.0	24.0	5.1
7	105	212	200	48	124	14	0.6	142.0	9.4	3.9	3.5	4.2	15.0	16.0	5.2
8	137	182	79	62	104	14	1.2	143.0	9.6	3.8	2.9	4.7	30.0	52.0	4.4
9	91	238	80	65	157	15	0.9	141.0	9.7	3.8	4.4	4.8	28.0	35.0	3.5
10	89	175	126	44	106	9	0.7	135.0	9.7	4.2	4.8	4.8	21.0	19.0	4.1
11	103	250	346	42	139	18	0.7	137.0	9.6	3.8	4.6	4.3	12.0	15.0	2.8
12	101	257	105	126	110	11	0.6	145.0	9.5	3.6	3.8	4.4	33.0	40.0	3.1
13	90	185	109	48	115	10	0.9	140.0	9.5	4.2	3.0	4.2	15.0	6.0	4.5
14	105	175	151	32	113	15	1.2	139.0	9.0	3.8	2.7	4.5	17.0	23.0	3.5
15	95	234	249	36	148	16	1.0	143.0	9.4	3.5	2.9	4.7	47.0	55.0	4.5
16	113	208	70	54	140	20	0.9	139.0	9.7	4.3	3.9	4.3	22.0	25.0	3.5
17	93	210	108	51	138	20	1.4	141.0	9.7	3.6	4.1	4.4	45.0	55.0	2.7
18	100	201	63	67	121	12	1.1	141.0	9.3	4.9	3.3	5.5	17.0	17.0	3.1
19	92	197	111	45	130	16	1.1	142.0	10.4	4.3	3.8	4.9	45.0	53.0	5.0
20	95	236	96	64	153	17	1.0	137.0	9.3	3.8	2.8	4.2	25.0	32.0	3.7
21	96	214	189	43	133	17	0.8	142.0	9.2	4.1	3.9	4.2	25.0	15.0	3.1
22	95	225	74	64	146	11	0.9	142.0	9.1	3.9	3.2	4.6	14.0	10.0	2.8
23	120	290	202	46	204	14	0.9	142.0	10.0	3.6	3.6	4.5	12.0	19.0	5.5
24	91	264	94	56	189	10	0.7	141.0	8.6	3.5	2.9	4.9	19.0	25.0	5.8
25	103	166	77	61	90	14	1.1	143.0	10.1	5.1	3.8	4.1	20.0	14.0	7.3

Appendix C: Office BP measurement of the screening visit and after placebo (at baseline) (n=25)

No.	Office BP at screening visit (mm Hg)				Office BP after placebo			
	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR
1	147	80	102	76	164	109	127	80
2	142	93	109	80	147	94	112	76
3	166	78	107	72	177	95	122	90
4	140	80	100	72	142	84	103	88
5	147	90	109	52	156	85	109	62
6	157	90	112	72	178	107	131	72
7	147	90	109	89	171	106	128	96
8	130	83	99	76	149	105	120	84
9	153	72	99	72	171	82	112	80
10	132	91	105	73	128	92	104	72
11	130	90	103	70	156	107	123	72
12	134	80	98	82	140	81	101	80
13	137	80	99	74	153	90	111	70
14	144	80	101	72	173	101	125	84
15	140	84	103	72	149	104	119	83
16	145	80	102	75	157	96	116	70
17	150	90	110	71	175	80	112	77
18	150	94	113	100	142	92	109	96
19	137	90	106	72	146	89	108	64
20	140	90	107	67	147	103	118	64
21	150	77	101	72	142	82	102	73
22	130	83	99	74	136	103	114	76
23	160	100	120	75	140	92	108	76
24	141	87	105	72	162	93	116	72
25	144	87	106	77	152	102	119	84

Appendix D: Office BP and 24-hour ABP measurement at baseline (n=25)

No.	Office BP				Average 24-hour				Average day-time				Average night-time			
	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR
1	164	109	127	80	164	110	128	90	168	113	131	94	146	98	114	78
2	147	94	112	76	152	111	125	81	157	112	127	83	136	107	117	74
3	177	95	122	90	153	106	122	87	155	106	123	90	148	106	120	77
4	142	84	103	88	140	92	108	78	147	115	126	80	132	66	88	76
5	156	85	109	62	138	99	112	80	143	100	115	84	119	95	103	64
6	178	107	131	72	156	90	112	79	156	90	112	86	156	90	112	59
7	171	106	128	96	155	111	126	85	155	111	126	86	155	110	125	83
8	149	105	120	84	133	87	102	77	134	86	102	83	132	88	103	57
9	171	82	112	80	147	113	124	82	148	111	124	90	145	116	126	62
10	128	92	104	72	134	101	112	72	137	103	114	80	127	95	106	62
11	156	107	123	72	126	86	99	82	127	85	99	85	112	91	98	58
12	140	81	101	80	131	85	100	73	132	84	100	77	129	72	91	62
13	153	90	111	70	155	85	108	72	154	83	107	70	156	85	109	61
14	173	101	125	84	163	97	119	78	166	99	121	79	147	86	106	72
15	149	104	119	83	123	85	98	93	127	86	100	91	120	78	92	82
16	157	96	116	70	141	78	99	79	143	82	103	77	133	74	94	70
17	175	80	112	77	142	69	93	70	146	83	104	73	131	68	89	63
18	142	92	109	96	143	78	100	96	144	80	101	102	135	71	92	77
19	146	89	108	64	130	85	100	65	133	82	99	79	122	74	90	52
20	147	103	118	64	133	85	101	59	130	77	95	60	142	65	91	49
21	142	82	102	73	148	88	108	89	150	82	105	89	140	82	101	89
22	136	103	114	76	124	87	100	64	124	80	95	67	124	82	96	52
23	140	92	108	76	128	85	99	82	133	89	104	85	114	74	88	73
24	162	93	116	72	138	91	107	63	138	95	110	65	139	86	104	60
25	152	102	119	84	131	85	100	72	128	86	100	77	139	81	100	63

Appendix E: 24-hour urine collection data of the individual subjects at baseline (n=25)

NO.	Creatinine excretion 24-hr (1000-2000 mg/24hr)	Sodium excretion 24-hr (40-220 mEq/24hr)	Calcium excretion 24-hr (50-250 mg/24hr)	% FENa	% FECal	Clcr (from urine collection)	Clcr (from Cockcroft and Gault)
1	1302.0	430.9	220.1	2.42	1.82	90.42	60.98
2	1518.0	213.9	50.6	1.31	0.43	81.09	61.81
3	792.0	94.5	73.8	0.85	0.97	55.00	37.23
4	1000.0	134.0	62.0	0.83	0.62	77.16	57.46
5	1160.0	82.0	71.0	0.67	0.88	61.96	46.40
6*	1051.0	95.9	111.5	0.71	1.23	66.40	60.10
7	1044.0	222.7	349.2	0.90	2.13	120.83	96.28
8	1876.0	253.8	229.6	1.14	1.53	108.60	77.60
9	459.0	89.1	10.8	1.24	0.22	35.42	24.15
10	1134.0	178.2	237.6	0.82	1.51	112.50	93.20
11	984.0	184.8	156.0	0.96	1.16	97.62	90.72
12	680.0	132.0	154.0	0.80	1.43	78.70	77.83
13*	855.0	139.5	126.0	1.05	1.40	65.97	74.57
14	1540.0	77.9	115.1	0.44	0.99	89.11	66.75
15	912.0	126.7	132.5	0.97	1.55	63.33	54.28
16	950.0	147.5	170.0	1.00	1.66	73.30	61.39
17*	916.5	113.2	50.8	1.23	0.80	45.46	40.86
18*	880.0	98.0	218.0	0.87	2.93	55.56	63.04
19	1323.0	144.0	99.0	0.84	0.79	83.52	65.14
20	1115.5	146.0	104.7	0.96	1.01	77.47	49.32
21	819.0	122.4	136.8	0.84	1.45	71.09	50.53
22	736.0	142.6	216.2	1.23	2.91	56.79	55.68
23	949.0	156.0	130.0	1.04	1.23	73.22	65.98
24	765.0	88.4	54.4	0.57	0.58	75.89	67.58
25	1062.4	114.5	93.0	0.83	0.95	67.07	47.46

* patients who had total creatinine in the 24-hour urine specimen fell below the normal range

Appendix F: Office Blood Pressure at baseline and after treatment with HCTZ or $CaCO_3$ alone

No.	Dose HCTZ/kg (mg)	Office Blood Pressure (mm Hg)								
		Baseline (n=25)			Group 1 (n=12) HCTZ 25 mg OD 4 weeks			Group 2 (n=13) $CaCO_3$ 1 gm BID 4 weeks		
		SBP	DBP	MAP	SBP	DBP	MAP	SBP	DBP	MAP
1	-	164	109	127				156	105	122
2	0.38	147	94	112	139	85	103			
3	0.48	177	95	122	156	80	105			
4	-	142	84	103				127	77	94
5	0.42	156	85	109	138	77	97			
6	0.37	178	107	131	166	94	118			
7	0.34	171	106	128	143	86	105			
8	-	149	105	120				163	103	123
9	0.80	171	82	112	136	76	96			
10	-	128	92	104				128	91	103
11	-	156	107	123				150	98	115
12	-	140	81	101				130	90	103
13	-	153	90	111				142	89	107
14	-	173	101	125				182	105	131
15	0.41	149	104	119	133	71	92			
16	0.43	157	96	116	155	96	116			
17	0.33	175	80	112	145	83	104			
18	0.38	142	92	109	143	88	106			
19	-	146	89	108				141	83	102
20	0.34	147	103	118	128	82	97			
21	-	142	82	102				149	84	106
22	-	136	103	114				139	98	112
23	-	140	92	108				140	86	104
24	0.52	162	93	116	156	89	111			
25	-	152	102	119				159	94	116

Appendix F: Office Blood Pressure at baseline, after $CaCO_3$ was added on HCTZ treatment in group 1 patients and after HCTZ was added on $CaCO_3$ treatment in group 2 patients

No.	Dose HCTZ/kg (mg)	Office Blood Pressure (mm Hg)								
		Baseline (n=25)			Group 1 (n=12) HCTZ 25 mg OD + $CaCO_3$ 1 gm BID			Group 2 (n=13) $CaCO_3$ 1 gm BID + HCTZ 25 mg OD		
		SBP	DBP	MAP	SBP	DBP	MAP	SBP	DBP	MAP
1	0.36	164	109	127				167	98	121
2	0.38	147	94	112	141	86	104			
3	0.48	177	95	122	155	86	109			
4	0.41	142	84	103				124	79	94
5	0.42	156	85	109	122	74	90			
6	0.37	178	107	131	144	91	109			
7	0.34	171	106	128	153	104	120			
8	0.32	149	105	120				164	103	123
9	0.80	171	82	112	138	70	93			
10	0.44	128	92	104				136	92	107
11	0.38	156	107	123				193	100	131
12	0.54	140	81	101				122	85	97
13	0.39	153	90	111				134	88	103
14	0.34	173	101	125				161	96	118
15	0.41	149	104	119	132	77	95			
16	0.43	157	96	116	152	86	108			
17	0.33	175	80	112	141	84	103			
18	0.38	142	92	109	118	78	91			
19	0.37	146	89	108				136	83	101
20	0.34	147	103	118	151	84	106			
21	0.47	142	82	102				128	98	108
22	0.48	136	103	114				130	90	103
23	0.41	140	92	108				111	85	94
24	0.52	162	93	116	159	100	120			
25	0.44	152	102	119				140	104	116

Appendix F: Reduction in Office Blood Pressure after treatment with HCTZ or $CaCO_3$ alone as compared to baseline and after combination of the two drugs as compared to one drug.

No.	Dose HCTZ/kg (mg)	Reduction in Office Blood Pressure (mm Hg)																	
		Group 1 (n=12)									Group 2 (n=13)								
		HCTZ vs baseline (1)			HCTZ + $CaCO_3$ vs baseline (2)			(2) – (1)			$CaCO_3$ vs baseline (3)			$CaCO_3$ + HCTZ vs baseline (4)			(4) – (3)		
		SBP	DBP	MAP	SBP	DBP	MAP	SBP	DBP	MAP	SBP	DBP	MAP	SBP	DBP	MAP	SBP	DBP	MAP
1	0.36										-8	-4	-5	3	-11	-6	11	-7	-1
2	0.38	-8	-9	-9	-6	-8	-8	2	1	1									
3	0.48	-21	-15	-17	-22	-9	-13	-1	6	4									
4	0.41										-15	-7	-9	-18	-5	-9	-3	2	0
5	0.42	-18	-8	-12	-34	-11	-19	-16	-3	-7									
6	0.37	-12	-13	-13	-34	-16	-22	-22	-3	-9									
7	0.34	-28	-20	-23	-18	-2	-8	10	18	15									
8	0.32										14	-2	3	15	-2	3	1	0	0
9	0.80	-35	-6	-16	-33	-12	-19	2	-6	-3									
10	0.44										0	-1	-1	8	0	3	8	1	4
11	0.38										-6	-9	-8	37	-7	8	43	2	16
12	0.54										-10	9	2	-18	4	-4	-8	-5	-6
13	0.39										-11	-1	-4	-19	-2	-8	-8	-1	-4
14	0.34										9	4	6	-12	-5	-7	-21	-9	-13
15	0.41	-16	-33	-27	-17	-27	-24	-1	6	4									
16	0.43	-2	0	0	-5	-10	-8	-3	-10	-8									
17	0.33	-30	3	-8	-34	4	-9	-4	1	-1									
18	0.38	1	-4	-3	-24	-14	-18	-25	-10	-15									
19	0.37										-5	-6	-6	-10	-6	-7	-5	0	-1
20	0.34	-19	-21	-21	4	-19	-12	23	2	9									
21	0.47										7	2	4	-14	16	6	-21	14	2
22	0.48										3	-5	-2	-6	-13	-11	-9	-8	-9
23	0.41										0	-6	-4	-29	-7	-14	-29	-1	-10
24	0.52	-6	-4	-5	-3	7	4	3	11	8									
25	0.44										7	-8	-3	-12	2	-3	-19	10	0

Appendix G: Average Ambulatory Blood Pressure at baseline and after treatment with HCTZ or $CaCO_3$ alone

No.	Dose HCTZ/kg (mg)	Average 24-hour Ambulatory Blood Pressure (mm Hg)								
		Baseline (n=25)			Group 1 (n=12) HCTZ 25 mg OD 4 weeks			Group 2 (n=13) $CaCO_3$ 1 gm BID 4 weeks		
		SBP	DBP	MAP	SBP	DBP	MAP	SBP	DBP	MAP
1	-	164	110	128				149	108	122
2	0.38	152	111	125	142	94	110			
3	0.48	153	106	122	122	68	86			
4	-	140	92	108				125	78	94
5	0.42	138	99	112	122	67	85			
6	0.37	156	90	112	152	115	127			
7	0.34	155	111	126	150	86	107			
8	-	133	87	102				142	87	105
9	0.80	147	113	124	113	80	91			
10	-	134	101	112				130	76	94
11	-	126	86	99				143	77	99
12	-	131	85	100				111	64	80
13	-	155	85	108				131	84	100
14	-	163	97	119				172	102	125
15	0.41	123	85	98	135	71	92			
16	0.43	141	78	99	154	85	108			
17	0.33	142	69	93	121	66	84			
18	0.38	143	78	100	139	78	98			
19	-	130	85	100				154	90	111
20	0.34	133	85	101	119	65	83			
21	-	148	88	108				133	76	95
22	-	124	87	100				140	92	109
23	-	128	85	99				139	86	104
24	0.52	138	91	107	128	83	98			
25	-	131	85	100				131	83	99

Appendix G: Average 24-hour Ambulatory Blood Pressure at baseline, after $CaCO_3$ was added on HCTZ treatment in group 1 patients and after HCTZ was added on $CaCO_3$ treatment in group 2 patients

No.	Dose HCTZ/kg (mg)	Average 24-hour Ambulatory Blood Pressure (mm Hg)								
		Baseline (n=25)			Group 1 (n=12) HCTZ 25 mg OD + $CaCO_3$ 1 gm BID			Group 2 (n=13) $CaCO_3$ 1 gm BID + HCTZ 25 mg OD		
		SBP	DBP	MAP	SBP	DBP	MAP	SBP	DBP	MAP
1	0.36	164	110	128				147	94	112
2	0.38	152	111	125	140	90	107			
3	0.48	153	106	122	138	74	95			
4	0.41	140	92	108				121	79	93
5	0.42	138	99	112	109	69	83			
6	0.37	156	90	112	131	77	95			
7	0.34	155	111	126	144	88	107			
8	0.32	133	87	102				157	93	114
9	0.80	147	113	124	153	74	100			
10	0.44	134	101	112				127	73	91
11	0.38	126	86	99				164	91	115
12	0.54	131	85	100				127	65	86
13	0.39	155	85	108				141	96	111
14	0.34	163	97	119				153	98	116
15	0.41	123	85	98	131	75	94			
16	0.43	141	78	99	145	91	109			
17	0.33	142	69	93	126	77	93			
18	0.38	143	78	100	127	74	92			
19	0.37	130	85	100				132	88	103
20	0.34	133	85	101	118	78	92			
21	0.47	148	88	108				128	74	92
22	0.48	124	87	100				126	84	98
23	0.41	128	85	99				103	68	80
24	0.52	138	91	107	132	89	103			
25	0.44	131	85	100				120	74	89

Appendix G: Reduction in 24-hour ambulatory Blood Pressure after treatment with HCTZ or $CaCO_3$ alone as compared to baseline and after combination of the two drugs as compared to one drug.

No.	Dose HCTZ/kg (mg)	Reduction in 24-hour Ambulatory Blood Pressure (mm Hg)																	
		Group 1 (n=12)									Group 2 (n=13)								
		HCTZ vs baseline (1)			HCTZ + $CaCO_3$ vs baseline (2)			(2) – (1)			$CaCO_3$ vs baseline (3)			$CaCO_3$ + HCTZ vs baseline (4)			(4) – (3)		
		SBP	DBP	MAP	SBP	DBP	MAP	SBP	DBP	MAP	SBP	DBP	MAP	SBP	DBP	MAP	SBP	DBP	MAP
1	0.36										-15	-2	-6	-17	-16	-16	-2	-14	-10
2	0.38	-10	-17	-15	-12	-21	-18	-2	-4	-3									
3	0.48	-31	-38	-36	-15	-32	-27	16	6	9									
4	0.41										-15	-14	-14	-19	-13	-15	-4	1	-1
5	0.42	-16	-32	-27	-29	-30	-29	-13	2	-2									
6	0.37	-4	25	15	-25	-13	-17	-21	-38	-32									
7	0.34	-5	-25	-19	-11	-23	-19	-6	2	0									
8	0.32										9	0	3	24	6	12	15	6	9
9	0.80	-34	-33	-33	6	-39	-24	40	-6	9									
10	0.44										-4	-25	-18	-7	-28	-21	-3	-3	-3
11	0.38										17	-9	0	38	5	16	21	14	16
12	0.54										-20	-21	-20	-4	-20	-14	16	1	6
13	0.39										-24	-1	-8	-14	11	3	10	12	11
14	0.34										9	5	6	-10	1	-3	-19	-4	-9
15	0.41	12	-14	-6	8	-10	-4	-4	4	2									
16	0.43	13	7	9	4	13	10	-9	6	1									
17	0.33	-21	-3	-9	-16	8	0	5	11	9									
18	0.38	-4	0	-2	-16	-4	-8	-12	-4	-6									
19	0.37										24	5	11	2	3	3	-22	-2	-8
20	0.34	-14	-20	-18	-15	-7	-9	-1	13	9									
21	0.47										-15	-12	-13	-20	-14	-16	-5	-2	-3
22	0.48										16	5	9	2	-3	-2	-14	-8	-11
23	0.41										11	1	5	-25	-17	-19	-36	-18	-24
24	0.52	-10	-8	-9	-6	-2	-4	4	6	5									
25	044										0	-2	-1	-11	-11	-11	-11	-9	-10

Appendix H: Average Day-time Ambulatory Blood Pressure at baseline and after treatment with HCTZ or $CaCO_3$ alone

No.	Dose HCTZ/kg (mg)	Average Day-time Ambulatory Blood Pressure (mm Hg)								
		Baseline (n=25)			Group 1 (n=12) HCTZ 25 mg OD 4 weeks			Group 2 (n=13) $CaCO_3$ 1 gm BID 4 weeks		
		SBP	DBP	MAP	SBP	DBP	MAP	SBP	DBP	MAP
1	-	168	113	131				152	110	124
2	0.38	157	112	127	141	93	109			
3	0.48	155	106	123	125	70	88			
4	-	147	115	126				127	81	96
5	0.42	143	100	115	130	68	89			
6	0.37	156	90	112	151	118	129			
7	0.34	155	111	126	149	85	106			
8	-	134	86	102				142	86	105
9	0.80	148	111	124	118	95	103			
10	-	137	103	114				135	81	99
11	-	127	85	99				145	81	102
12	-	132	84	100				118	73	88
13	-	154	83	107				131	83	99
14	-	166	99	121				171	101	124
15	0.41	127	86	100	135	72	93			
16	0.43	143	82	103	154	84	107			
17	0.33	146	83	104	124	71	89			
18	0.38	144	80	101	140	78	99			
19	-	133	82	99				156	91	113
20	0.34	130	77	95	123	69	87			
21	-	150	82	105				135	77	96
22	-	124	80	95				143	92	109
23	-	133	89	104				144	88	107
24	0.52	138	95	110	127	83	98			
25	-	128	86	100				130	84	99

Appendix H: Average Day-time Ambulatory Blood Pressure at baseline, after $CaCO_3$ was added on HCTZ treatment in group 1 patients and after HCTZ was added on $CaCO_3$ treatment in group 2 patients

No.	Dose HCTZ/kg (mg)	Average Day-time Ambulatory Blood Pressure (mm Hg)								
		Baseline (n=25)			Group 1 (n=12) HCTZ 25 mg OD + $CaCO_3$ 1 gm BID			Group 2 (n=13) $CaCO_3$ 1 gm BID + HCTZ 25 mg OD		
		SBP	DBP	MAP	SBP	DBP	MAP	SBP	DBP	MAP
1	0.36	168	113	131				152	90	111
2	0.38	157	112	127	144	86	105			
3	0.48	155	106	123	147	84	105			
4	0.41	147	115	126				120	79	93
5	0.42	143	100	115	113	70	85			
6	0.37	156	90	112	129	78	95			
7	0.34	155	111	126	145	90	108			
8	0.32	134	86	102				160	96	117
9	0.80	148	111	124	153	77	102			
10	0.44	137	103	114				129	78	95
11	0.38	127	85	99				170	96	121
12	0.54	132	84	100				129	64	86
13	0.39	154	83	107				141	98	112
14	0.34	166	99	121				154	100	118
15	0.41	127	86	100	135	77	97			
16	0.43	143	82	103	145	98	114			
17	0.33	146	83	104	132	83	99			
18	0.38	144	80	101	131	77	95			
19	0.37	133	82	99				137	90	106
20	0.34	130	77	95	117	84	95			
21	0.47	150	82	105				132	75	94
22	0.48	124	80	95				127	84	98
23	0.41	133	89	104				104	70	82
24	0.52	138	95	110	131	89	103			
25	0.44	128	86	100				122	75	91

Appendix H: Reduction in Day-time Ambulatory Blood Pressure after treatment with HCTZ or $CaCO_3$ alone as compared to baseline and after combination of the two drugs as compared to one drug.

No.	Dose HCTZ/kg (mg)	Reduction in Day-time Ambulatory Blood Pressure (mm Hg)																	
		Group 1 (n=12)									Group 2 (n=13)								
		HCTZ vs baseline (1)			HCTZ + $CaCO_3$ vs baseline (2)			(2) – (1)			$CaCO_3$ vs baseline (3)			$CaCO_3$ + HCTZ vs baseline (4)			(4) – (3)		
		SBP	DBP	MAP	SBP	DBP	MAP	SBP	DBP	MAP	SBP	DBP	MAP	SBP	DBP	MAP	SBP	DBP	MAP
1	0.36										-16	-3	-7	-16	-23	-20	0	-20	-13
2	0.38	-16	-19	-18	-13	-26	-22	3	-7	-4									
3	0.48	-30	-36	-35	-8	-22	-18	22	14	17									
4	0.41										-20	-34	-30	-27	-36	-33	-7	-2	-3
5	0.42	-13	-32	-26	-30	-30	-30	-17	2	-4									
6	0.37	-5	28	17	-27	-12	-17	-22	-40	-34									
7	0.34	-6	-26	-20	-10	-21	-18	-4	5	2									
8	0.32										8	0	3	26	10	15	18	10	12
9	0.80	-30	-16	-21	5	-34	-22	35	-18	-1									
10	0.44										-2	-22	-15	-8	-25	-19	-6	-3	-4
11	0.38										18	-4	3	43	11	22	25	15	19
12	0.54										-14	-11	-12	-3	-20	-14	11	-9	-2
13	0.39										-23	0	-8	-13	15	5	10	15	13
14	0.34										5	2	3	-12	1	-3	-17	-1	-6
15	0.41	8	-14	-7	8	-9	-3	0	5	4									
16	0.43	11	2	4	2	16	11	-9	14	7									
17	0.33	-22	-12	-15	-14	0	-5	8	12	10									
18	0.38	-4	-2	-2	-13	-3	-6	-9	-1	-4									
19	0.37										23	9	14	4	8	7	-19	-1	-7
20	0.34	-7	-8	-8	-13	7	0	-6	15	8									
21	0.47										-15	-5	-9	-18	-7	-11	-3	-2	-2
22	0.48										19	12	14	3	4	3	-16	-8	-11
23	0.41										11	-1	3	-29	-19	-22	-40	-18	-25
24	0.52	-11	-12	-12	-7	-6	-7	4	6	5									
25	0.44										2	-2	-1	-6	-11	-9	-8	-9	-8

No.	Dose HCTZ/kg (mg)	Average Night-time Ambulatory Blood Pressure (mm Hg)								
		Baseline (n=25)			Group 1 (n=12) HCTZ 25 mg OD 4 weeks			Group 2 (n=13) $CaCO_3$ 1 gm BID 4 weeks		
		SBP	DBP	MAP	SBP	DBP	MAP	SBP	DBP	MAP
1	-	146	98	114				142	101	115
2	0.38	136	107	117	129	87	101			
3	0.48	148	106	120	113	63	80			
4	-	132	66	88				119	70	86
5	0.42	119	95	103	103	67	79			
6	0.37	156	90	112	153	104	120			
7	0.34	155	110	125	151	86	108			
8	-	132	88	103				135	96	109
9	0.80	145	116	126	110	66	81			
10	-	127	95	106				108	63	78
11	-	112	91	98				138	57	84
12	-	129	72	91				108	60	76
13	-	156	85	109				131	91	104
14	-	147	86	106				172	102	125
15	0.41	120	78	92	136	65	89			
16	0.43	133	74	94	155	90	112			
17	0.33	131	68	89	107	62	77			
18	0.38	135	71	92	128	69	89			
19	-	122	74	90				148	87	107
20	0.34	142	65	91	108	54	72			
21	-	140	82	101				129	72	91
22	-	124	82	96				136	93	108
23	-	114	74	88				124	81	96
24	0.52	139	86	104	130	83	99			
25	-	139	81	100				135	80	98

Appendix I: Average Night-time Ambulatory Blood Pressure at baseline, after $CaCO_3$ was added on HCTZ treatment in group 1 patients and after HCTZ was added on $CaCO_3$ treatment in group 2 patients

No.	Dose HCTZ/kg (mg)	Average Night-time Ambulatory Blood Pressure (mm Hg)								
		Baseline (n=25)			Group 1 (n=12) HCTZ 25 mg OD + $CaCO_3$ 1 gm BID			Group 2 (n=13) $CaCO_3$ 1 gm BID + HCTZ 25 mg OD		
		SBP	DBP	MAP	SBP	DBP	MAP	SBP	DBP	MAP
1	0.36	146	98	114				140	90	107
2	0.38	136	107	117	122	83	96			
3	0.48	148	106	120	126	70	88			
4	0.41	132	66	88				119	64	82
5	0.42	119	95	103	97	66	77			
6	0.37	156	90	112	139	70	93			
7	0.34	155	110	125	141	83	102			
8	0.32	132	88	103				148	83	105
9	0.80	145	116	126	150	63	92			
10	0.44	127	95	106				109	70	83
11	0.38	112	91	98				147	79	102
12	0.54	129	72	91				120	61	81
13	0.39	156	85	109				145	83	104
14	0.34	147	86	106				147	91	110
15	0.41	120	78	92	119	69	86			
16	0.43	133	74	94	147	76	100			
17	0.33	131	68	89	116	69	85			
18	0.38	135	71	92	116	65	82			
19	0.37	122	74	90				119	79	92
20	0.34	142	65	91	123	51	75			
21	0.47	140	82	101				120	71	87
22	0.48	124	82	96				121	84	96
23	0.41	114	74	88				101	62	75
24	0.52	139	86	104	134	89	104			
25	0.44	139	81	100				113	74	87

Appendix I: Reduction in Night-time Ambulatory Blood Pressure after treatment with HCTZ or $CaCO_3$ alone as compared to baseline and after combination of the two drugs as compared to one drug.

No.	Dose HCTZ/kg (mg)	Reduction in Night-time Ambulatory Blood Pressure (mm Hg)																	
		Group 1 (n=12)									Group 2 (n=13)								
		HCTZ vs baseline (1)			HCTZ + $CaCO_3$ vs baseline (2)			(2) – (1)			$CaCO_3$ vs baseline (3)			$CaCO_3$ + HCTZ vs baseline (4)			(4) – (3)		
		SBP	DBP	MAP	SBP	DBP	MAP	SBP	DBP	MAP	SBP	DBP	MAP	SBP	DBP	MAP	SBP	DBP	MAP
1	0.36										-4	3	1	-6	-8	-7	-2	-11	-8
2	0.38	-7	-20	-16	-14	-24	-21	-7	-4	-5									
3	0.48	-35	-43	-40	-22	-36	-32	13	7	8									
4	0.41										-13	4	-2	-13	-2	-6	0	-6	-4
5	0.42	-16	-28	-24	-22	-29	-26	-6	-1	-2									
6	0.37	-3	14	8	-17	-20	-19	-14	-34	-27									
7	0.34	-4	-24	-17	-14	-27	-23	-10	-3	-6									
8	0.32										3	8	6	16	-5	2	13	-13	-4
9	0.80	-35	-50	-45	5	-53	-34	40	-3	11									
10	0.44										-19	-32	-28	-18	-25	-23	1	7	5
11	0.38										26	-34	-14	35	-12	4	9	22	18
12	0.54										-21	-12	-15	-9	-11	-10	12	1	5
13	0.39										-25	6	-5	-11	-2	-5	14	-8	0
14	0.34										25	16	19	0	5	4	-25	-11	-15
15	0.41	16	-13	-3	-1	-9	-6	-17	4	-3									
16	0.43	22	16	18	14	2	6	-8	-14	-12									
17	0.33	-24	-6	-12	-15	1	-4	9	7	8									
18	0.38	-7	-2	-3	-19	-6	-10	-12	-4	-7									
19	0.37										26	13	17	-3	5	2	-29	-8	-15
20	0.34	-34	-11	-19	-19	-14	-16	15	-3	3									
21	0.47										-11	-10	-10	-20	-11	-14	-9	-1	-4
22	0.48										12	11	12	-3	2	0	-15	-9	-12
23	0.41										10	7	8	-13	-12	-13	-23	-19	-21
24	0.52	-9	-3	-5	-5	3	0	4	6	5									
25	0.44										-4	-1	-2	-26	-7	-13	-22	-6	-11

Appendix J: Blood Pressure Loads at baseline and after treatment with HCTZ or $CaCO_3$ alone

No.	Blood Pressure Loads (%)																	
	Baseline (n=25)						Group 1 (n=12) HCTZ 25 mg OD for 4 weeks						Group 2 (n=13) $CaCO_3$ 1 gm BID for 4 weeks					
	24-hour		Day-time		Night-time		24-hour		Day-time		Night-time		24-hour		Day-time		Night-time	
	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP
1	83	93	91	94	100	88							67	92	67	89	100	100
2	83	98	97	100	100	100	55	64	50	58	100	100						
3	77	90	80	87	100	100	8	5	10	7	22	0						
4	58	92	67	100	100	90							9	21	12	28	50	13
5	47	68	56	70	43	71	29	3	41	5	11	0						
6	80	49	81	46	100	67	69	92	67	90	100	100						
7	83	97	84	97	100	100	71	46	68	47	100	78						
8	32	43	32	43	63	63							38	54	42	50	100	100
9	69	89	65	85	100	100	14	5	60	45	80	70						
10	25	100	70	40	80	30							50	25	50	30	50	0
11	25	38	27	36	0	100							51	28	50	35	78	11
12	33	33	36	41	63	50							11	11	22	12	10	5
13	72	36	68	32	100	75							23	13	22	11	67	100
14	86	69	90	72	83	67							100	87	100	90	100	100
15	40	27	31	23	100	50	28	8	26	10	75	0						
16	42	16	48	21	89	11	94	43	93	39	100	86						
17	56	18	64	24	56	0	10	0	14	0	0	0						
18	50	12	58	15	89	11	61	29	77	36	67	22						
19	24	15	27	15	50	13							69	41	70	45	89	56
20	41	3	36	4	89	0	18	7	25	10	25	0						
21	50	15	65	26	85	40							30	11	29	14	78	0
22	8	13	10	13	56	78							37	59	46	54	94	100
23	26	18	34	21	33	11							43	35	54	43	56	67
24	47	47	48	72	94	83	18	16	17	21	78	89						
25	35	9	32	12	100	67							30	27	32	32	100	44

ppendix J: Blood Pressure Loads at baseline, after $CaCO_3$ was added on HCTZ treatment in group 1 patients and after HCTZ was added on $CaCO_3$ treatment in group 2 patients

No.	Blood Pressure Loads (%)																	
	Baseline (n=25)						Group 1 (n=12) HCTZ 25 mg OD + $CaCO_3$ 1 gm BID						Group 2 (n=13) $CaCO_3$ 1 gm BID + HCTZ 25 mg OD					
	24-hour		Day-time		Night-time		24-hour		Day-time		Night-time		24-hour		Day-time		Night-time	
	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP
1	83	93	91	94	100	88							50	50	56	44	100	100
2	83	98	97	100	100	100	53	60	55	60	100	100						
3	77	90	80	87	100	100	37	0	50	0	67	22						
4	58	92	67	100	100	90							29	36	25	33	50	50
5	47	68	56	70	43	71	11	7	15	10	0	0						
6	80	49	81	46	100	67	43	21	42	25	100	50						
7	83	97	84	97	100	100	68	49	71	61	100	78						
8	32	43	32	43	63	63							74	68	85	85	100	56
9	69	89	65	85	100	100	59	8	57	11	78	0						
10	25	100	70	40	80	30							31	14	41	19	22	11
11	25	38	27	36	0	100							84	66	91	78	89	56
12	33	33	36	41	63	50							23	5	29	6	44	0
13	72	36	68	32	100	75							74	42	68	45	100	33
14	86	69	90	72	83	67							82	68	85	73	100	75
15	40	27	31	23	100	50	25	11	33	15	44	11						
16	42	16	48	21	89	11	53	58	54	69	100	33						
17	56	18	64	24	56	0	16	18	22	30	28	11						
18	50	12	58	15	89	11	21	12	25	17	22	11						
19	24	15	27	15	50	13							31	36	40	47	44	22
20	41	3	36	4	89	0	25	38	29	43	100	0						
21	50	15	65	26	85	40							20	16	30	23	53	20
22	8	13	10	13	56	78							16	24	21	21	56	67
23	26	18	34	21	33	11							5	3	3	3	10	0
24	47	47	48	72	94	83	26	32	22	33	71	86						
25	35	9	32	12	100	67							8	16	10	14	22	22

Appendix J: Reduction in 24-hour Blood Pressure Loads (%) after treatment with HCTZ or $CaCO_3$ alone as compared to baseline and after combination of the two drugs as compared to one drug.

No.	Reduction in 24-hour Blood Pressure Loads (%)											
	Group 1 (n=12)						Group 2 (n=13)					
	HCTZ vs baseline (1)		HCTZ + $CaCO_3$ vs baseline (2)		(2) – (1)		$CaCO_3$ vs baseline (3)		$CaCO_3$ + HCTZ vs baseline (4)		(4) – (3)	
	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP
1							-16	-1	-33	-43	-17	-42
2	-28	-34	-30	-38	-2	-4						
3	-69	-85	-40	-90	29	-5						
4							-49	-71	-29	-56	20	15
5	-18	-65	-36	-61	-18	4						
6	-11	43	-37	-28	-26	-71						
7	-12	-51	-15	-48	-3	3						
8							6	11	42	25	36	14
9	-55	-84	-10	-81	45	3						
10							25	-75	6	-86	-19	-11
11							26	-10	59	28	33	38
12							-22	-22	-10	-28	12	-6
13							-49	-23	2	6	51	29
14							14	18	-4	-1	-18	-19
15	-12	-19	-15	-16	-3	3						
16	52	27	11	42	-41	15						
17	-46	-18	-40	0	6	18						
18	11	17	-29	0	-40	-17						
19							45	26	7	21	-38	-5
20	-23	4	-16	35	7	31						
21							-20	-4	-30	1	-10	5
22							29	46	8	11	-21	-35
23							17	17	-21	-15	-38	-32
24	-29	-31	-21	-15	8	16						
25							-5	18	-27	7	-22	-11

Appendix K: Reduction in Day-time Blood Pressure Loads (%) after treatment with HCTZ or $CaCO_3$ alone as compared to baseline and after combination of the two drugs as compared to one drug.

No.	Reduction in Day-time Blood Pressure Loads (%)											
	Group 1 (n=12)						Group 2 (n=13)					
	HCTZ vs baseline (1)		HCTZ + $CaCO_3$ vs baseline (2)		(2) – (1)		$CaCO_3$ vs baseline (3)		$CaCO_3$ + HCTZ vs baseline (4)		(4) – (3)	
	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP
1							-24	-5	-35	-50	-11	-45
2	-47	-42	-42	-40	5	2						
3	-70	-80	-30	-87	40	-7						
4							-55	-72	-42	-67	13	5
5	-15	-65	-41	-60	-26	5						
6	-14	44	-39	-21	-25	-65						
7	-16	-50	-13	-36	3	14						
8							10	7	53	42	43	35
9	-5	-40	-8	-74	-3	-34						
10							-20	-10	-29	-21	-9	-11
11							23	-1	64	42	41	43
12							-14	-29	-7	-35	7	-6
13							-46	-21	0	13	46	34
14							10	18	-5	1	-15	-17
15	-5	-13	2	-8	7	5						
16	45	18	6	48	-39	30						
17	-50	-24	-42	6	8	30						
18	19	21	-33	2	-52	-19						
19							43	30	13	32	-30	2
20	-11	6	-7	39	4	33						
21							-36	-12	-35	-3	1	9
22							36	41	11	8	-25	-33
23							20	22	-31	-18	-51	-40
24	-31	-51	-26	-39	5	12						
25							0	20	-22	2	-22	-18

Appendix L: Reduction in Night-time Blood Pressure Loads (%) after treatment with HCTZ or $CaCO_3$ alone as compared to baseline and after combination of the two drugs as compared to one drug.

No.	Reduction in Night-time Blood Pressure Loads (%)											
	Group 1 (n=12)						Group 2 (n=13)					
	HCTZ vs baseline (1)		HCTZ + $CaCO_3$ vs baseline (2)		(2) – (1)		$CaCO_3$ vs baseline (3)		$CaCO_3$ + HCTZ vs baseline (4)		(4) – (3)	
	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP
1							0	12	0	12	0	0
2	0	0	0	0	0	0						
3	-78	-100	-33	-78	45	22						
4							-50	-77	-50	-40	0	37
5	-32	-71	-43	-71	-11	0						
6	0	33	0	-17	0	-50						
7	0	-22	0	-22	0	0						
8							37	37	37	-7	0	-44
9	-20	-30	-22	-100	-2	-70						
10							-30	-30	-58	-19	-28	11
11							78	-89	89	-44	11	45
12							-53	-45	-19	-50	34	-5
13							-33	25	0	-42	33	-67
14							17	33	17	8	0	-25
15	-25	-50	-56	-39	-31	11						
16	11	75	11	22	0	-53						
17	-56	0	-28	11	28	11						
18	-22	11	-67	0	-45	-11						
19							39	43	-6	9	-45	-34
20	-64	0	11	0	75	0						
21							-7	-40	-32	-20	-25	20
22							38	22	0	-11	-38	-33
23							23	56	-23	-11	-46	-67
24	-16	6	-23	3	-7	-3						
25							0	-23	-78	-45	-78	-22

Appendix M: Nocturnal decline in BP (%) and classification after treatment with HCTZ or $CaCO_3$ alone

No.	Nocturnal decline in BP (%)																	
	Baseline (n=25)						Group 1 (n=12) HCTZ 25 mg OD for 4 weeks						Group 2 (n=13) $CaCO_3$ 1 gm BID for 4 weeks					
	SBP		DBP		MAP		SBP		DBP		MAP		SBP		DBP		MAP	
	%	class	%	class	%	class	%	class	%	class	%	class	%	class	%	class	%	class
1	13.1	D	13.3	D	13.0	D							6.6	ND	8.2	ND	7.3	ND
2	13.4	D	4.5	ND	7.9	ND	8.5	ND	6.5	ND	7.3	ND						
3	4.5	ND	0.0	ND	2.4	ND	10.0	D	10.0	D	10.0	D						
4	10.2	D	42.6	ED	30.0	ED							6.3	ND	13.6	D	10.4	D
5	16.8	D	5.0	ND	10.4	D	20.8	ED	1.5	ND	11.2	D						
6	0.0	ND	0.0	ND	0.0	ND	-1.3	ID	11.9	D	7.0	ND						
7	0.0	ND	0.9	ND	0.8	ND	-1.3	ID	-1.2	ID	-1.9	ID						
8	1.5	ND	-2.3	ID	-1.0	ID							4.9	ND	-11.6	ID	-3.8	ID
9	2.0	ND	-4.5	ID	-1.6	ID	6.8	ND	30.5	ED	21.4	ED						
10	7.3	ND	7.8	ND	7.0	ND							20.0	ED	22.2	ED	21.2	ED
11	11.8	D	-7.1	ID	1.0	ND							4.8	ND	29.6	ED	17.6	D
12	2.3	ND	14.3	D	9.0	ND							8.5	ND	17.8	D	13.6	D
13	-1.3	ID	-2.4	ID	-1.9	ID							0.0	ND	-9.6	ID	-5.1	ID
14	11.4	D	13.1	D	12.4	D							-0.6	ID	-1.0	ID	-0.8	ID
15	5.5	ND	9.3	ND	8.0	ND	-0.7	ID	9.7	ND	4.3	ND						
16	7.0	ND	9.8	ND	8.7	ND	-0.6	ID	-7.1	ID	-4.7	ID						
17	10.3	D	18.1	D	14.4	D	13.7	D	12.7	D	13.5	D						
18	6.3	ND	11.3	D	8.9	ND	8.6	ND	11.5	D	10.1	D						
19	8.3	ND	9.8	ND	9.1	ND							5.1	ND	4.4	ND	5.3	ND
20	-9.2	ID	15.6	D	4.2	ND	12.2	D	21.7	ED	17.2	D						
21	6.7	ND	0.0	ND	3.8	ND							4.4	ND	6.5	ND	5.2	ND
22	0.0	ND	-2.5	ID	-1.1	ID							4.9	ND	-1.1	ID	0.9	ND
23	14.3	D	16.9	D	15.4	D							13.9	D	8.0	ND	10.3	D
24	-0.7	ID	9.5	ND	5.5	ND	-2.4	ID	0.0	ND	-1.0	ID						
25	-8.6	ID	5.8	ND	0.0	ND							-3.8	ID	4.8	ND	1.0	ND

Appendix M: Nocturnal decline in BP (%) and classification at baseline, after $CaCO_3$ was added on HCTZ treatment in group 1 patients and after HCTZ was added on $CaCO_3$ treatment in group 2 patients

No.	Nocturnal decline in BP (%)																	
	Baseline (n=25)						Group 1 (n=12) HCTZ 25 mg OD + $CaCO_3$ 1 gm BID						Group 2 (n=13) $CaCO_3$ 1 gm BID + HCTZ 25 mg OD					
	SBP		DBP		MAP		SBP		DBP		MAP		SBP		DBP		MAP	
	%	class	%	class	%	class	%	class	%	class	%	class	%	class	%	class	%	class
1	13.1	D	13.3	D	13.0	D							7.9	ND	0.0	ND	3.6	ND
2	13.4	D	4.5	ND	7.9	ND	15.3	D	3.5	ND	8.6	ND						
3	4.5	ND	0.0	ND	2.4	ND	14.3	D	16.7	D	16.2	D						
4	10.2	D	42.6	ED	30.0	ED							0.8	ND	19.0	D	11.8	D
5	16.8	D	5.0	ND	10.4	D	14.2	D	5.7	ND	10.0	D						
6	0.0	ND	0.0	ND	0.0	ND	-7.8	ID	10.3	D	2.1	ND						
7	0.0	ND	0.9	ND	0.8	ND	2.8	ND	7.8	ND	5.5	ND						
8	1.5	ND	-2.3	ID	-1.0	ID							7.5	ND	13.5	D	10.3	D
9	2.0	ND	-4.5	ID	-1.6	ID	2.0	ND	18.2	D	10.0	D						
10	7.3	ND	7.8	ND	7.0	ND							15.5	D	10.3	D	12.6	D
11	11.8	D	-7.1	ID	1.0	ND							13.5	D	17.7	D	15.7	D
12	2.3	ND	14.3	D	9.0	ND							7.0	ND	4.7	ND	5.8	ND
13	-1.3	ID	-2.4	ID	-1.9	ID							-2.8	ID	15.3	D	7.1	ND
14	11.4	D	13.1	D	12.4	D							4.5	ND	9.0	ND	6.8	ND
15	5.5	ND	9.3	ND	8.0	ND	11.9	D	10.4	D	11.3	D						
16	7.0	ND	9.8	ND	8.7	ND	-1.4	ID	22.4	ED	12.3	D						
17	10.3	D	18.1	D	14.4	D	12.1	D	16.9	D	14.1	D						
18	6.3	ND	11.3	D	8.9	ND	11.5	D	15.6	D	13.7	D						
19	8.3	ND	9.8	ND	9.1	ND							13.1	D	12.2	D	13.2	D
20	-9.2	ID	15.6	D	4.2	ND	-5.1	ID	39.3	ED	21.1	ED						
21	6.7	ND	0.0	ND	3.8	ND							9.1	ND	5.3	ND	7.4	ND
22	0.0	ND	-2.5	ID	-1.1	ID							4.7	ND	0.0	ND	2.0	ND
23	14.3	D	16.9	D	15.4	D							2.9	ND	11.4	D	8.5	ND
24	-0.7	ID	9.5	ND	5.5	ND	-2.3	ID	0.0	ND	-1.0	ID						
25	-8.6	ID	5.8	ND	0.0	ND							7.4	ND	1.3	ND	4.0	ND

Appendix N: 24-hour urine collection data after treatment with HCTZ or $CaCO_3$ alone (n=25)

NO.	Creatinine excretion 24-hr (1000-2000 mg/24hr)	Sodium excretion 24-hr (40-220 mEq/24hr)	Calcium excretion 24-hr (50-250 mg/24hr)	% FENa	% FECal	Clcr (from urine collection)	Clcr (from Cockcroft and Gault)
1	1380.0	312.8	271.4	1.63	1.97	95.83	60.98
2	1425.0	179.5	107.5	1.17	0.98	76.12	61.81
3	744.0	70.7	41.9	0.82	0.68	43.06	31.03
4	914.3	96.3	185.3	0.65	1.82	70.60	57.46
5	1383.2	279.3	71.8	1.88	0.72	73.90	46.40
6	1400.0	112.0	134.4	0.69	1.15	81.02	55.06
7	1008.0	312.1	424.2	1.54	3.24	100.00	82.53
8	1798.0	197.2	391.5	0.86	2.44	113.50	84.70
9	475.0	77.5	15.0	1.17	0.35	32.99	21.73
10	1120.0	193.2	282.8	0.73	1.55	129.62	108.80
11	936.0	100.8	183.6	0.71	1.84	72.22	70.56
12	798.0	147.0	178.5	0.93	1.57	79.17	66.72
13	945.0	135.0	142.5	1.01	1.51	65.63	67.11
14	1396.5	165.9	202.2	1.03	1.74	80.82	66.75
15	877.8	115.1	49.0	0.83	0.53	67.73	60.31
16	931.0	190.0	150.1	1.46	1.65	64.65	55.25
17	1157.3	148.3	14.7	1.37	0.19	57.41	38.13
18	1012.0	185.6	193.2	1.43	2.26	63.89	63.04
19	1338.8	187.6	166.3	0.88	1.06	103.29	79.61
20	1110.0	132.8	34.5	1.06	0.39	64.24	41.10
21	762.5	98.8	96.3	0.91	1.36	52.95	40.42
22	783.0	130.5	223.3	1.18	3.17	54.38	50.11
23	915.0	141.5	125.7	0.87	1.12	79.43	74.22
24	920.0	154.1	64.4	0.94	0.60	79.86	59.13
25	1064.0	198.8	120.4	1.58	1.33	61.57	43.51

Appendix N: 24-hour urine collection data after $CaCO_3$ was added on HCTZ treatment in group 1 patients and after HCTZ was added on $CaCO_3$ treatment in group 2 patients (n=25)

NO.	Creatinine excretion 24-hr (1000-2000 mg/24hr)	Sodium excretion 24-hr (40-220 mEq/24hr)	Calcium excretion 24-hr (50-250 mg/24hr)	% FENa	% FECal	Clcr (from urine collection)	Clcr (from Cockcroft and Gault)
1	1105.0	282.0	188.9	1.64	1.62	85.26	67.75
2	1353.0	223.8	126.84	2.04	1.59	55.27	47.26
3	705.5	98.6	51.9	1.39	1.00	35.00	26.59
4	840.0	156.8	173.6	1.23	1.94	64.81	57.46
5	1216.0	172.8	384.0	1.34	4.28	64.96	46.40
6	1131.0	153.1	175.7	1.08	1.74	71.40	60.10
7	1026.0	349.6	326.8	1.45	1.99	118.75	96.28
8	1430.0	185.0	274.0	0.84	1.82	110.30	103.50
9	441.0	63.0	25.2	1.13	0.71	27.84	19.76
10	976.0	206.4	260.8	1.20	2.11	84.72	81.56
11	1044.0	100.3	190.8	0.57	1.64	90.63	79.38
12	740.0	144.0	160.0	0.83	1.32	85.65	77.84
13	978.5	244.4	117.8	1.79	1.23	67.94	67.11
14	1479.8	118.6	128.4	0.67	1.14	85.64	86.75
15	1040.3	115.4	57.7	0.78	0.59	72.24	54.28
16	873.2	75.5	136.2	0.56	1.45	67.38	61.39
17	1108.8	201.6	47.9	1.78	0.59	55.00	40.86
18	999.0	206.9	268.8	1.01	1.94	99.10	99.07
19	1306.6	141.9	98.7	1.09	1.07	64.81	51.18
20	1228.4	300.4	304.9	1.95	2.87	77.55	44.84
21	1179.2	137.3	161.9	0.96	1.81	68.24	33.69
22	787.4	188.0	231.1	1.53	2.75	60.76	55.68
23	1001.0	27.3	82.6	0.19	0.86	69.51	59.38
24	756.0	163.8	132.3	1.20	1.41	65.63	59.13
25	1008.0	145.6	145.6	1.03	1.40	70.00	52.21

Appendix O: Comparison of office BP and 24- hour ABP after treatment with hydrochlorothiazide or $CaCO_3$ alone as compared to baseline and after combination of the two drugs as compared to one drug when the patients were classified as dippers/non-dippers according to nocturnal reduction of baseline SBP

Parameter	Comparison of office BP and 24-hour ABP (mm Hg)											
	Non-dipper (n=17)						Dipper (n=8)					
	Group 1 (n=9)			Group 2 (n=8)			Group 1 (n=3)			Group 2 (n=5)		
	HCTZ vs baseline (1)[a]	HCTZ+$CaCO_3$ vs baseline (2)[a]	(2)-(1)[b]	$CaCO_3$ vs baseline (3)[a]	$CaCO_3$+HCTZ vs baseline (4)[a]	(4)-(3)[b]	HCTZ vs baseline (1)[a]	HCTZ+$CaCO_3$ vs baseline (2)[a]	(2)-(1)[b]	$CaCO_3$ vs baseline (3)[a]	$CaCO_3$+HCTZ vs baseline (4)[b]	(4)-(3)[b]
Office BP (mean ± SD)												
SBP (mm Hg)	$\downarrow 15^{**}$	$\downarrow 17^{**}$	$\downarrow 2^{+}$	$\uparrow 1^{+}$	$\downarrow 7^{++++}$	$\downarrow 8^{*}$	$\downarrow 19^{++++}$	$\downarrow 25^{++++}$	$\downarrow 6^{+}$	$\downarrow 4^{+}$	$\downarrow 4^{+}$	$\leftrightarrow^{+}$
DBP (mm Hg)	$\downarrow 13^{**}$	$\downarrow 12^{**}$	$\uparrow 1^{+}$	$\downarrow 2^{+}$	$\downarrow 1^{+}$	$\uparrow 1^{+}$	$\downarrow 4^{+}$	$\downarrow 5^{+}$	$\downarrow 1^{+}$	$\downarrow 4^{++++}$	$\downarrow 7^{**}$	$\downarrow 3^{+}$
MAP (mm Hg)	$\downarrow 14^{**}$	$\downarrow 14^{**}$	$\leftrightarrow^{+}$	$\downarrow 1^{+}$	$\downarrow 3^{++}$	$\downarrow 2^{++}$	$\downarrow 9^{*}$	$\downarrow 12^{++++}$	$\downarrow 3^{+}$	$\downarrow 4^{+++}$	$\downarrow 6^{++++}$	$\downarrow 2^{+}$
24-hour ABP (mean ± SD)												
-average 24-hour												
SBP (mm Hg)	$\downarrow 8^{++++}$	$\downarrow 8^{++++}$	$\leftrightarrow^{+}$	$\downarrow 2^{+}$	$\downarrow 4^{+}$	$\downarrow 2^{+}$	$\downarrow 16^{*}$	$\downarrow 19^{++++}$	$\downarrow 3^{+}$	$\uparrow 1^{+}$	$\downarrow 7^{+}$	$\downarrow 8^{+}$
DBP (mm Hg)	$\downarrow 12^{++++}$	$\downarrow 13^{*}$	$\downarrow 1^{+}$	$\downarrow 6^{+++}$	$\downarrow 7^{++++}$	$\downarrow 1^{+}$	$\downarrow 17^{++++}$	$\downarrow 14^{+}$	$\uparrow 3^{+}$	$\downarrow 4^{+}$	$\downarrow 8^{+++}$	$\downarrow 4^{+}$
MAP (mm Hg)	$\downarrow 10^{++++}$	$\downarrow 11^{*}$	$\downarrow 1^{+}$	$\downarrow 5^{++}$	$\downarrow 6^{++++}$	$\downarrow 1^{+}$	$\downarrow 17^{++++}$	$\downarrow 16^{+++}$	$\uparrow 1^{+}$	$\downarrow 2^{+}$	$\downarrow 8^{+}$	$\downarrow 6^{+}$
-average day-time												
SBP (mm Hg)	$\downarrow 8^{++++}$	$\downarrow 7^{++++}$	$\uparrow 1^{+}$	$\downarrow 1^{+}$	$\downarrow 2^{+}$	$\downarrow 1^{+}$	$\downarrow 17^{*}$	$\downarrow 19^{++++}$	$\downarrow 2^{+}$	$\downarrow 1^{+}$	$\downarrow 8^{+}$	$\downarrow 7^{+}$
DBP (mm Hg)	$\downarrow 9^{++++}$	$\downarrow 9^{++++}$	$\leftrightarrow^{+}$	$\downarrow 2^{+}$	$\downarrow 3^{+}$	$\downarrow 1^{+}$	$\downarrow 21^{++++}$	$\downarrow 19^{++++}$	$\uparrow 2^{+}$	$\downarrow 8^{++}$	$\downarrow 13^{+++}$	$\downarrow 5^{+}$
MAP (mm Hg)	$\downarrow 9^{++++}$	$\downarrow 9^{*}$	$\leftrightarrow^{+}$	$\downarrow 2^{+}$	$\downarrow 3^{+}$	$\downarrow 1^{+}$	$\downarrow 20^{*}$	$\downarrow 19^{++++}$	$\uparrow 1^{+}$	$\downarrow 5^{+}$	$\downarrow 11^{+}$	$\downarrow 6^{+}$
-average night-time												
SBP (mm Hg)	$\downarrow 10^{+++}$	$\downarrow 9^{++++}$	$\uparrow 1^{+}$	$\downarrow 5^{+}$	$\downarrow 9^{++++}$	$\downarrow 4^{+}$	$\downarrow 16^{++++}$	$\downarrow 17^{*}$	$\downarrow 1^{+}$	$\uparrow 8^{+}$	$\leftrightarrow^{+}$	$\downarrow 8^{++}$
DBP (mm Hg)	$\downarrow 13^{++++}$	$\downarrow 18^{*}$	$\downarrow 5^{++}$	$\downarrow 2^{+}$	$\downarrow 7^{++++}$	$\downarrow 5^{++++}$	$\downarrow 18^{++++}$	$\downarrow 18^{+++}$	$\leftrightarrow^{+}$	$\downarrow 1^{+}$	$\downarrow 6^{+++}$	$\downarrow 5^{+}$
MAP (mm Hg)	$\downarrow 12^{++++}$	$\downarrow 15^{**}$	$\downarrow 3^{+}$	$\downarrow 3^{+}$	$\downarrow 8^{*}$	$\downarrow 5^{+++}$	$\downarrow 17^{*}$	$\downarrow 17^{++++}$	$\leftrightarrow^{+}$	$\uparrow 2^{+}$	$\downarrow 4^{+}$	$\downarrow 6^{+}$

a versus baseline of each group, b versus before combined second drug

*** p<0.001, ** p<0.01, *p<0.05, ++++ p=0.05-0.10, +++ p=0.11-0.20, ++ p=0.21-0.30, + p>0.31

Appendix P: Comparison of office BP and 24- hour ABP after treatment with hydrochlorothiazide or $CaCO_3$ alone as compared to baseline and after combination of the two drugs as compared to one drug when the patients were classified as dippers/non-dippers according to nocturnal reduction of baseline DBP

Parameter	Comparison of office BP and 24-hour ABP (mm Hg)											
	Non-dipper (n=17)						Dipper (n=8)					
	Group 1 (n=9)			Group 2 (n=8)			Group 1 (n=3)			Group 2 (n=5)		
	HCTZ vs baseline (1)[a]	HCTZ+$CaCO_3$ vs baseline (2)[a]	(2)-(1)[b]	$CaCO_3$ vs baseline (3)[a]	$CaCO_3$+HCTZ vs baseline (4)[a]	(4)-(3)[b]	HCTZ vs baseline (1)[a]	HCTZ+$CaCO_3$ vs baseline (2)[a]	(2)-(1)[b]	$CaCO_3$ vs baseline (3)[a]	$CaCO_3$+HCTZ vs baseline (4)[b]	(4)-(3)[b]
Office BP (mean ± SD)												
SBP (mm Hg)	$\downarrow 16^{**}$	$\downarrow 19^{**}$	$\downarrow 3^{+}$	$\uparrow 1^{+}$	$\downarrow 1^{+}$	$\downarrow 2^{+}$	$\downarrow 16^{++}$	$\downarrow 18^{++}$	$\downarrow 2^{+}$	$\downarrow 5^{+}$	$\downarrow 15^{*}$	$\downarrow 10^{++}$
DBP (mm Hg)	$\downarrow 12^{**}$	$\downarrow 10^{**}$	$\uparrow 2^{+}$	$\downarrow 4^{*}$	$\downarrow 2^{+}$	$\uparrow 2^{+}$	$\downarrow 7^{+}$	$\downarrow 10^{++}$	$\downarrow 3^{+}$	$\downarrow 1^{+}$	$\downarrow 5^{++++}$	$\downarrow 4^{++++}$
MAP (mm Hg)	$\downarrow 14^{***}$	$\downarrow 13^{**}$	$\uparrow 1^{+}$	$\downarrow 2^{++}$	$\downarrow 1^{+}$	$\uparrow 1^{+}$	$\downarrow 10^{+++}$	$\downarrow 13^{*}$	$\downarrow 3^{+}$	$\downarrow 2^{+}$	$\downarrow 8^{*}$	$\downarrow 6^{++++}$
24-hour ABP (mean ± SD)												
-average 24-hour												
SBP (mm Hg)	$\downarrow 9^{++++}$	$\downarrow 9^{++++}$	$\leftrightarrow^{+}$	$\uparrow 3^{+}$	$\uparrow 2^{+}$	$\downarrow 1^{+}$	$\downarrow 13^{++++}$	$\downarrow 16^{***}$	$\downarrow 3^{+}$	$\downarrow 6^{+}$	$\downarrow 15^{*}$	$\downarrow 9^{+}$
DBP (mm Hg)	$\downarrow 15^{++++}$	$\downarrow 17^{*}$	$\downarrow 2^{+}$	$\downarrow 4^{++}$	$\downarrow 4^{+}$	$\leftrightarrow^{+}$	$\downarrow 8^{+}$	$\downarrow 1^{+}$	$\uparrow 7^{+}$	$\downarrow 6^{++}$	$\downarrow 13^{*}$	$\downarrow 7^{++++}$
MAP (mm Hg)	$\downarrow 13^{*}$	$\downarrow 15^{**}$	$\downarrow 2^{+}$	$\downarrow 2^{+}$	$\downarrow 2^{+}$	$\leftrightarrow^{+}$	$\downarrow 9^{++++}$	$\downarrow 6^{+++}$	$\uparrow 3^{+}$	$\downarrow 6^{+}$	$\downarrow 14^{**}$	$\downarrow 8^{+++}$
-average day-time												
SBP (mm Hg)	$\downarrow 10^{++++}$	$\downarrow 9^{++++}$	$\uparrow 1^{+}$	$\uparrow 4^{+}$	$\uparrow 4^{+}$	$\leftrightarrow^{+}$	$\downarrow 11^{++++}$	$\downarrow 13^{**}$	$\downarrow 2^{+}$	$\downarrow 7^{+}$	$\downarrow 17^{*}$	$\downarrow 10^{++}$
DBP (mm Hg)	$\downarrow 14^{++++}$	$\downarrow 16^{*}$	$\downarrow 2^{+}$	$\downarrow 2^{+}$	$\leftrightarrow^{+}$	$\uparrow 2^{+}$	$\downarrow 7^{++++}$	$\uparrow 1^{+}$	$\uparrow 8^{++}$	$\downarrow 9^{++}$	$\downarrow 19^{*}$	$\downarrow 10^{++++}$
MAP (mm Hg)	$\downarrow 13^{**}$	$\downarrow 14^{**}$	$\downarrow 1^{+}$	$\leftrightarrow^{+}$	$\uparrow 1^{+}$	$\uparrow 1^{+}$	$\downarrow 9^{++++}$	$\downarrow 4^{++}$	$\uparrow 5^{+}$	$\downarrow 8^{++}$	$\downarrow 18^{*}$	$\downarrow 10^{++++}$
-average night-time												
SBP (mm Hg)	$\downarrow 8^{++}$	$\downarrow 9^{++++}$	$\downarrow 1^{+}$	$\uparrow 1^{+}$	$\downarrow 4^{+}$	$\downarrow 5^{+}$	$\downarrow 22^{++++}$	$\downarrow 18^{**}$	$\uparrow 4^{+}$	$\uparrow 1^{+}$	$\downarrow 8^{*}$	$\downarrow 7^{+}$
DBP (mm Hg)	$\downarrow 17^{*}$	$\downarrow 21^{**}$	$\downarrow 4^{++}$	$\downarrow 5^{+}$	$\downarrow 7^{++++}$	$\downarrow 2^{+}$	$\downarrow 6^{+++}$	$\downarrow 6^{++}$	$\leftrightarrow^{+}$	$\uparrow 4^{+}$	$\downarrow 6^{++++}$	$\downarrow 10^{*}$
MAP (mm Hg)	$\downarrow 14^{++++}$	$\downarrow 17^{**}$	$\downarrow 3^{+}$	$\downarrow 3^{+}$	$\downarrow 6^{++++}$	$\downarrow 3^{+}$	$\downarrow 12^{++++}$	$\downarrow 10^{++++}$	$\uparrow 2^{+}$	$\uparrow 2^{+}$	$\downarrow 7^{++++}$	$\downarrow 9^{+++}$

a versus baseline of each group, b versus before combined second drug

*** p<0.001, ** p<0.01, *p<0.05, ++++ p=0.05-0.10, +++ p=0.11-0.20, ++ p=0.21-0.30, + p>0.31

Appendix Q: Comparison of frequency of BP loads (%) after treatment with hydrochlorothiazide or $CaCO_3$ alone as compared to baseline and after combination of the two drugs as compared to one drug when patients were classified as dippers/non-dippers according to nocturnal reduction of baseline SBP

	Comparison of frequency of BP loads (%)											
	Non-dipper (n=17)						Dipper (n=8)					
	Group 1 (n=9)			Group 2 (n=8)			Group 1 (n=3)			Group 2 (n=5)		
	HCTZ vs baseline (1)[a]	HCTZ+$CaCO_3$ vs baseline (2)[a]	(2)-(1)[b]	$CaCO_3$ vs baseline (3)[a]	$CaCO_3$+HCTZ vs baseline (4)[a]	(4)-(3)[b]	HCTZ vs baseline (1)[a]	HCTZ+$CaCO_3$ vs baseline (2)[a]	(2)-(1)[b]	$CaCO_3$ vs baseline (3)[a]	$CaCO_3$+HCTZ vs baseline (4)[b]	(4)-(3)[b]
24-hour BP loads												
SBP	$\downarrow 16^{+++}$	$\downarrow 19^{**}$	$\downarrow 3^{+}$	$\uparrow 1^{+}$	$\downarrow 1^{+}$	$\downarrow 2^{+}$	$\downarrow 30^{++++}$	$\downarrow 35^{**}$	$\downarrow 5^{+}$	$\downarrow 2^{+}$	$\downarrow 6^{+}$	$\downarrow 4^{+}$
DBP	$\downarrow 20^{++}$	$\downarrow 22^{++++}$	$\downarrow 2^{+}$	$\downarrow 3^{+}$	$\downarrow 6^{+}$	$\downarrow 3^{+}$	$\downarrow 39^{++++}$	$\downarrow 33^{+++}$	$\uparrow 6^{+}$	$\downarrow 9^{+}$	$\downarrow 17^{++}$	$\downarrow 8^{+}$
Day-time BP loads												
SBP	$\downarrow 10^{+}$	$\downarrow 16^{*}$	$\downarrow 6^{+}$	$\downarrow 4^{+}$	$\downarrow 2^{+}$	$\uparrow 2^{+}$	$\downarrow 37^{++++}$	$\downarrow 42^{***}$	$\downarrow 5^{+}$	$\downarrow 5^{+}$	$\downarrow 10^{+}$	$\downarrow 5^{+}$
DBP	$\downarrow 16^{++}$	$\downarrow 20^{++}$	$\downarrow 4^{+}$	$\uparrow 3^{+}$	$\uparrow 5^{+}$	$\uparrow 2^{+}$	$\downarrow 43^{++++}$	$\downarrow 31^{++}$	$\uparrow 12^{++}$	$\downarrow 8^{+}$	$\downarrow 18^{+}$	$\downarrow 10^{+}$
Night-time BP loads												
SBP	$\downarrow 24^{*}$	$\downarrow 20^{++++}$	$\uparrow 4^{+}$	$\downarrow 2^{+}$	$\downarrow 19^{++++}$	$\downarrow 17^{++}$	$\downarrow 29^{++}$	$\downarrow 24^{++}$	$\uparrow 5^{+}$	$\uparrow 13^{+}$	$\uparrow 7^{+}$	$\downarrow 6^{+}$
DBP	$\downarrow 9^{+}$	$\downarrow 26^{++++}$	$\downarrow 17^{+++}$	$\downarrow 2^{+}$	$\downarrow 23^{*}$	$\downarrow 21^{++++}$	$\downarrow 24^{+}$	$\downarrow 20^{+}$	$\uparrow 4^{+}$	$\downarrow 13^{+}$	$\downarrow 15^{++}$	$\downarrow 2^{+}$

a versus baseline of each group, b versus before combined second drug

*** p<0.001, ** p<0.01, *p<0.05, ++++ p=0.05-0.10, +++ p=0.11-0.20, ++ p=0.21-0.30, + p>0.31

Appendix R: Comparison of frequency of BP loads (%) after treatment with hydrochlorothiazide or $CaCO_3$ alone as compared to baseline and after combination of the two drugs as compared to one drug when patients were classified as dippers/non-dippers according to nocturnal reduction of baseline DBP

	Comparison of frequency of BP loads (%)											
	Non-dipper (n=17)						Dipper (n=8)					
	Group 1 (n=9)			Group 2 (n=8)			Group 1 (n=3)			Group 2 (n=5)		
	HCTZ vs baseline (1)[a]	HCTZ+$CaCO_3$ vs baseline (2)[a]	(2)-(1)[b]	$CaCO_3$ vs baseline (3)[a]	$CaCO_3$+HCTZ vs baseline (4)[a]	(4)-(3)[b]	HCTZ vs baseline (1)[a]	HCTZ+$CaCO_3$ vs baseline (2)[a]	(2)-(1)[b]	$CaCO_3$ vs baseline (3)[a]	$CaCO_3$+HCTZ vs baseline (4)[b]	(4)-(3)[b]
24-hour BP loads												
SBP	$\downarrow 20^{++++}$	$\downarrow 22^{**}$	$\downarrow 2^{+}$	$\uparrow 7^{+}$	$\uparrow 8^{+}$	$\uparrow 1^{+}$	$\downarrow 19^{+}$	$\downarrow 28^{*}$	$\downarrow 9^{+}$	$\downarrow 11^{+}$	$\downarrow 19^{*}$	$\downarrow 8^{+}$
DBP	$\downarrow 33^{*}$	$\downarrow 37^{*}$	$\downarrow 4^{+}$	$\downarrow 1^{+}$	$\uparrow 1^{+}$	$\uparrow 2^{+}$	$\uparrow 1^{+}$	$\uparrow 11^{+}$	$\uparrow 10^{+}$	$\downarrow 12^{+}$	$\downarrow 29^{*}$	$\downarrow 17^{++++}$
Day-time BP loads												
SBP	$\downarrow 17^{++++}$	$\downarrow 21^{**}$	$\downarrow 4^{+}$	$\uparrow 2^{+}$	$\uparrow 7^{+}$	$\uparrow 5^{+}$	$\downarrow 14^{+}$	$\downarrow 27^{++++}$	$\downarrow 13^{+}$	$\downarrow 13^{+}$	$\downarrow 24^{*}$	$\downarrow 11^{+}$
DBP	$\downarrow 31^{*}$	$\downarrow 35^{*}$	$\downarrow 4^{+}$	$\uparrow 6^{+}$	$\uparrow 14^{+++}$	$\uparrow 8^{+}$	$\uparrow 1^{+}$	$\uparrow 15^{+}$	$\uparrow 14^{+}$	$\downarrow 13^{+}$	$\downarrow 34^{*}$	$\downarrow 21^{++++}$
Night-time BP loads												
SBP	$\downarrow 18^{++++}$	$\downarrow 18^{*}$	$\leftrightarrow^{+}$	$\uparrow 15^{+}$	$\downarrow 6^{+}$	$\downarrow 21^{++++}$	$\downarrow 47^{++++}$	$\downarrow 28^{+}$	$\uparrow 19^{+}$	$\downarrow 12^{+}$	$\downarrow 15^{++}$	$\downarrow 3^{+}$
DBP	$\downarrow 18^{+}$	$\downarrow 34^{*}$	$\downarrow 16^{++++}$	$\downarrow 7^{+}$	$\downarrow 22^{*}$	$\downarrow 15^{++}$	$\uparrow 3^{+}$	$\uparrow 3^{+}$	$\leftrightarrow^{+}$	$\downarrow 4^{+}$	$\downarrow 16^{++}$	$\downarrow 12^{+}$

a versus baseline of each group, b versus before combined second drug

*** p<0.001, ** p<0.01, *p<0.05, ++++ p=0.05-0.10, +++ p=0.11-0.20, ++ p=0.21-0.30, + p>0.31

Appendix S: Percentage of nocturnal reduction of BP at baseline and after treatment with HCTZ and $CaCO_3$ alone and when used the two drugs in combination when the patients were classified as dippers/non-dippers according to nocturnal reduction of baseline SBP

	Percentage of nocturnal reduction of BP					
	Group 1 (n=12)				Group 2 (n=13)	
	Baseline	HCTZ[a]	HCTZ + $CaCO_3$[a,b]		Baseline	$CaCO_3$[a]	$CaCO_3$ + HCTZ[a,b]
SBP[f] (mean ± SD)				SBP[f] (mean ± SD)			
non-dippers (n=9)	1.70 ± 5.03	3.48 ± 5.81^{+}	2.86 ± 7.96$^{+,+}$	non-dippers (n=8)	2.01 ± 5.56	5.50 ± 6.95^{+}	7.68 ± 5.52$^{++++,++}$
dippers (n=3)	13.48 ± 3.26	14.33 ± 6.17^{+}	13.85 ± 1.60$^{+,+}$	dippers (n=5)	12.17 ± 1.57	6.20 ± 5.19*	5.94 ± 4.97$^{*,+}$
DBP[g] (mean ± SD)				DBP[g] (mean ± SD)			
non-dippers (n=9)	5.75 ± 6.75	9.67 ± 11.62^{+}	15.62 ± 11.05$^{*,++++}$	non-dippers (n=8)	3.80 ± 6.50	4.18 ± 11.85^{+}	7.84 ± 5.77$^{++++,+}$
dippers (n=3)	9.18 ± 7.71	6.90 ± 5.61^{+}	8.69 ± 7.17$^{+,+}$	dippers (n=5)	15.76 ± 17.72	11.68 ± 11.30^{+}	11.42 ± 7.63$^{+,+}$
MAP[h] (mean ± SD)				MAP[h] (mean ± SD)			
non-dippers (n=9)	4.10 ± 3.94	6.93 ± 8.78^{+}	10.14 ± 6.92$^{*,++}$	non-dippers (n=8)	3.12 ± 4.71	4.79 ± 8.85^{+}	7.82 ± 3.98$^{*,+}$
dippers (n=3)	10.92 ± 3.29	10.67 ± 3.13^{+}	10.90 ± 2.86$^{+,+}$	dippers (n=5)	14.35 ± 10.36	8.96 ± 6.64^{+}	9.30 ± 4.66$^{+,+}$

a versus baseline of each group, b versus before combined second drug

f,g,h = nocturnal reduction of SBP, DBP and MAP, respectively (%)

*** p<0.001, ** p<0.01, *p<0.05, ++++ p=0.05-0.10, +++ p=0.11-0.20, ++ p=0.21-0.30, + p>0.31

Appendix T: Percentage of nocturnal reduction of BP at baseline and after treatment with HCTZ and $CaCO_3$ alone and when used the two drugs in combination when the patients were classified as dippers/non-dippers according to nocturnal reduction of baseline DBP

	Percentage of nocturnal reduction of BP					
	Group 1 (n=12)			Group 2 (n=13)		
	Baseline	HCTZ[a]	HCTZ + $CaCO_3$[a,c]	*Baseline*	$CaCO_3$[b]	$CaCO_3$ + HCTZ[b,d]
SBP[f] (mean ± SD)				SBP[f] (mean ± SD)		
non-dippers (n=9)	5.39 ± 6.16	$4.42 \pm 7.79^{+}$	$5.43 \pm 8.60^{+,+}$	non-dippers (n=8)	3.21 ± 6.56	$5.04 \pm 6.84^{+}$	$8.50 \pm 5.87^{+++,+++}$
dippers (n=3)	2.43 ± 10.30	$11.50 \pm 2.62^{++++}$	$6.15 \pm 9.77^{+,+}$	dippers (n=5)	10.26 ± 4.73	$6.94 \pm 5.20^{+}$	$4.63 \pm 2.90^{+++,+}$
DBP[g] (mean ± SD)				DBP[g] (mean ± SD)		
non-dippers (n=9)	3.82 ± 5.08	$6.87 \pm 10.83^{+}$	$10.55 \pm 7.33^{*,+}$	non-dippers (n=8)	1.13 ± 5.93	$5.65 \pm 14.27^{+}$	$9.46 \pm 6.54^{*,+}$
dippers (n=3)	14.97 ± 3.45	$15.30 \pm 5.57^{+}$	$23.91 \pm 13.33^{+,++++}$	dippers (n=5)	20.03 ± 12.71	$9.32 \pm 7.07^{+++}$	$8.82 \pm 7.16^{*,+}$
MAP[h] (mean ± SD)				MAP[h] (mean ± SD)		
non-dippers (n=9)	4.68 ± 4.37	$5.96 \pm 8.00^{+}$	$8.34 \pm 5.31^{+++,+}$	non-dippers (n=8)	2.12 ± 4.09	$5.29 \pm 9.51^{+}$	$9.06 \pm 4.74^{**,+++}$
dippers (n=3)	9.18 ± 5.11	$13.60 \pm 3.55^{++}$	$16.28 \pm 4.14^{+++,+++}$	dippers (n=5)	15.95 ± 8.17	$8.16 \pm 5.48^{+++}$	$7.32 \pm 3.07^{*,+}$

a versus baseline of each group, b versus before combined second drug

f,g,h = nocturnal reduction of SBP, DBP and MAP, respectively (%)

*** p<0.001, ** p<0.01, *p<0.05, ++++ p=0.05-0.10, +++ p=0.11-0.20, ++ p=0.21-0.30, + p>0.31

Appendix U: Laboratory data 24-hour excretion of urine of the dippers/non-dippers subjects at baseline and after treatment with hydrochlorothiazide or $CaCO_3$ alone and when used the two drugs in combination[1]

Test (normal range)	Baseline	HCTZ + $CaCO_3$[a]	Dippers / Non-dippers group based on nocturnal reduction of baseline DBP					
			Group 1			Group 2		
			Baseline	HCTZ[a]	HCTZ + $CaCO_3$[a,b]	Baseline	$CaCO_3$[a]	$CaCO_3$ + HCTZ[a,b]
Non-dippers (mean ± SD)	(n=15)	(n=15)	(n=8)	(n=8)	(n=8)	(n=7)	(n=7)	(n=7)
Creatinine (1000-2000 mg/24 hr)	1035.63 ± 345.84	1009.48 ± 268.04^{+}	950.00 ± 311.05	970.50 ± 313.46^{+}	926.38 ± 293.99$^{+,++}$	1133.49 ± 381.12	1114.61 ± 361.88^{+}	1104.46 ± 216.95$^{+,+}$
Sodium (40-220 mEq/24 hr)	147.01 ± 53.37	157.80 ± 71.02^{+}	133.09 ± 57.11	172.29 ± 88.05^{+++}	157.81 ± 94.47$^{+,+}$	162.91 ± 47.83	158.13 ± 46.28^{+}	157.79 ± 36.84$^{+,+}$
Calcium (50-250 mg/24 hr)	138.70 ± 89.99	173.59 ± 103.89^{+++}	114.04 ± 107.23	115.49 ± 131.48^{+}	155.11 ± 131.24$^{+,+}$	166.88 ± 61.19	209.17 ± 101.63^{++++}	194.70 ± 64.16$^{**,+}$
% FENa	0.94 ± 0.21	1.14 ± 0.39^{++++}	0.94 ± 0.25	1.23 ± 0.38^{+++}	1.24 ± 0.45$^{+++,+}$	0.95 ± 0.17	0.98 ± 0.31^{+}	1.03 ± 0.29$^{+,+}$
% FECal	1.25 ± 0.69	1.71 ± 0.90^{++++}	1.05 ± 0.67	1.09 ± 0.95^{+}	1.63 ± 1.17$^{++,+}$	1.47 ± 0.69	1.82 ± 0.74*	1.80 ± 0.54$^{**,+}$
Clcr (from laboratory) (ml/min)	77.60 ± 23.67	70.43 ± 23.95*	70.85 ± 24.72	67.29 ± 21.11^{+}	63.38 ± 27.52$^{+++,+}$	85.31 ± 21.54	83.93 ± 31.11^{+}	78.49 ± 17.69$^{+++,+}$
Clcr (from calculation) (ml/min)	61.96 ± 20.68	57.89 ± 23.83^{+++}	56.14 ± 21.65	52.27 ± 19.07^{+++}	51.39 ± 23.42$^{++++,+}$	68.62 ± 18.83	68.24 ± 25.05^{+}	65.31 ± 23.75$^{+,+}$
Dippers (mean ± SD)	(n=6)	(n=6)	(n=1)	(n=1)	(n=1)	(n=5)	(n=5)	(n=5)
Creatinine (1000-2000 mg/24 hr)	1097.75 ± 297.93	1065.70 ± 268.59^{+}	1115.50	1110.00	1228.40	1094.20 ± 332.96	1080.76 ± 284.77^{+}	1033.16 ± 286.77$^{+,+}$
Sodium (40-220 mEq/24 hr)	179.46 ± 126.12	171.52 ± 103.33^{+}	146.00	132.75	300.44	186.16 ± 139.81	172.70 ± 82.38^{+}	145.74 ± 91.46$^{+,+}$
Calcium (50-250 mg/24 hr)	130.98 ± 53.25	173.07 ± 74.81^{+}	104.70	34.50	304.88	136.23 ± 57.77	192.62 ± 52.51^{++++}	146.70 ± 42.21$^{+,*}$
% FENa	1.08 ± 0.69	1.08 ± 0.65^{+}	0.96	1.06	1.95	1.11 ± 0.77	1.02 ± 0.37^{+}	0.91 ± 0.55$^{+,+}$
% FECal	1.18 ± 0.41	1.63 ± 0.72^{++}	1.01	0. 39	2.87	1.22 ± 0.45	1.64 ± 0.33^{+++}	1.38 ± 0.42$^{+,++++}$
Clcr (from laboratory) (ml/min)	81.01 ± 7.04	78.07 ± 9.12^{+}	77.47	64.24	77.55	81.72 ± 7.62	81.17 ± 9.14^{+}	78.17 ± 10.19$^{+,+}$
Clcr (from calculation) (ml/min)	63.05 ± 9.64	65.67 ± 15.08^{+}	49.32	41.10	44.84	65.80 ± 7.72	65.23 ± 6.39^{+}	69.84 ± 12.42$^{+,+}$

1 After excluded 4 patients

a versus baseline of each group; b versus before combined second drugs

*** p<0.001, ** p<0.01, *p<0.05, ++++ p=0.05-0.10, +++ p=0.11-0.20, ++ p=0.21-0.30, + p>0.31

Appendix V: Laboratory data 24-hour excretion of urine of the dippers/non-dippers subjects at baseline and after treatment with hydrochlorothiazide or $CaCO_3$ alone and when used the two drugs in combination

Test (normal range)	Baseline	HCTZ + $CaCO_3$ [a]	Dippers / Non-dippers group based on nocturnal reduction of baseline MAP					
			Group 1			Group 2		
			Baseline	HCTZ [a]	HCTZ + $CaCO_3$ [a,b]	Baseline	$CaCO_3$ [a]	$CaCO_3$ + HCTZ [a,b]
Non-dippers (mean ± SD)	(n=16)	(n=16)	(n=8)	(n=8)	(n=8)	(n=8)	(n=8)	(n=8)
Creatinine (1000-2000 mg/24 hr)	1010.62 ± 344.66	993.41 ± 268.28^{+}	944.44 ± 307.13	936.35 ± 274.55^{+}	927.93 ± 295.77$^{+,+}$	1076.80 ± 387.57	1075.04 ± 353.24^{+}	1058.90 ± 238.64$^{+,+}$
Sodium (40-220 mEq/24 hr)	150.07 ± 48.80	164.91 ± 77.50^{+}	141.09 ± 53.29	153.98 ± 77.18^{+}	173.76 ± 107.26$^{++,+}$	159.04 ± 45.61	156.74 ± 43.02^{+}	156.06 ± 34.45$^{+,+}$
Calcium (50-250 mg/24 hr)	141.76 ± 85.65	167.79 ± 90.82^{+++}	118.25 ± 105.95	110.83 ± 133.89^{+}	145.23 ± 113.28$^{+,+}$	165.27 ± 56.83	205.34 ± 94.72^{++++}	190.36 ± 60.66$^{**,+}$
% FENa	0.95 ± 0.19	1.16 ± 0.43^{++++}	0.97 ± 0.23	1.12 ± 0.27^{+++}	1.31 ± 0.52$^{++++,+}$	0.93 ± 0.16	0.97 ± 0.28^{+}	1.01 ± 0.29$^{+,+}$
% FECal	1.27 ± 0.66	1.60 ± 0.64^{++++}	1.07 ± 0.66	1.05 ± 0.98^{+}	1.45 ± 0.74$^{++,+}$	1.47 ± 0.64	1.79 ± 0.69*	1.74 ± 0.52$^{*,+}$
Clcr (from laboratory) (ml/min)	78.63 ± 22.48	72.17 ± 23.43*	72.79 ± 24.53	66.08 ± 20.96^{++++}	64.96 ± 27.98$^{++++,+}$	84.49 ± 20.08	83.34 ± 28.85^{+}	79.39 ± 16.57$^{++,+}$
Clcr (from calculation) (ml/min)	63.14 ± 20.23	59.04 ± 23.61^{+++}	56.50 ± 21.49	51.61 ± 19.39^{++++}	51.19 ± 23.48$^{*,+}$	69.77 ± 17.74	68.05 ± 23.20^{+}	66.88 ± 22.43$^{+,+}$
Dippers (mean ± SD)	(n=5)	(n=5)	(n=1)	(n=1)	(n=1)	(n=4)	(n=4)	(n=4)
Creatinine (1000-2000 mg/24 hr)	1190.20 ± 239.86	1128.36 ± 240.37^{+}	1160.00	1383.20	1216.00	1197.75 ± 276.28	1151.45 ± 273.52^{+}	1106.45 ± 271.73$^{+++,+}$
Sodium (40-220 mEq/24 hr)	176.16 ± 146.29	151.50 ± 92.23^{+}	82.00	279.30	172.80	199.69 ± 157.61	179.12 ± 93.67^{+}	146.18 ± 105.60$^{+,+}$
Calcium (50-250 mg/24 hr)	119.63 ± 63.06	191.50 ± 115.35^{+}	71.00	71.82	384.00	131.79 ± 65.71	196.15 ± 59.94^{++++}	143.38 ± 47.97$^{+,*}$
% FENa	1.08 ± 0.78	1.01 ± 0.58^{+}	0.67	1.88	1.34	1.18 ± 0.86	1.04 ± 0.42^{+}	0.93 ± 0.63$^{+,+}$
% FECal	1.11 ± 0.45	1.97 ± 1.36^{++}	0.88	0.72	4.28	1.17 ± 0.37	1.66 ± 0.37^{+++}	1.39 ± 0.48$^{+,++++}$
Clcr (from laboratory) (ml/min)	78.37 ± 11.81	74.04 ± 10.59^{+++}	61.96	73.90	64.96	82.48 ± 8.58	81.67 ± 10.47^{+}	76.30 ± 10.73$^{++++,++}$
Clcr (from calculation) (ml/min)	59.51 ± 8.25	63.55 ± 15.03^{+}	46.40	46.40	46.40	62.79 ± 4.38	64.85 ± 7.32^{+}	67.83 ± 13.38$^{+,+}$

1 After excluded 4 patients

a versus baseline of each group; b versus before combined second drugs

*** p<0.001, ** p<0.01, *p<0.05, ++++ p=0.05-0.10, +++ p=0.11-0.20, ++ p=0.21-0.30, + p>0.31

Appendix W: Laboratorydata of the individual subjects after treatment with two drugs in combination (n=25)

NO.	FBS (60-100 mg/dl)	TC (150-220mg/dl)	TG (40-155 mg/dl)	HDL (50-100 mg/dl)	LDL (130-159 mg/dl)	BUN (5-20 mg/dl)	Cr (0.5-1.2 mg/dl)	Na 135-150 mEq/l)	Cal (9-11 mg/dl)	K (3.5-5.0 mg/dl)	phosphate (2.5-4.8 mg/dl)	Alb (3.8-5.0 g/dl)	SGOT (0.38 U/l)	SGPT (0-38 U/l)	uric acid (2.0-7.0 mg/dl)
1	106	200	250	34	116	10.0	0.9	140.0	9.5	4.4	3.6	4.2	20.0	25.0	3.2
2	95	195	110	35	138	19.0	1.7	138.0	10.0	3.3	2.8	4.7	18.0	20.0	3.9
3	98	176	106	68	87	20.0	1.4	141.0	10.3	3.4	3.0	4.5	28.0	30.0	2.9
4	98	248	167	58	157	13.0	0.9	137.0	9.6	3.8	3.6	4.2	26.0	34.0	3.1
5	101	185	90	59	108	11.0	1.3	138.0	9.6	3.5	3.9	5.7	28.0	27.0	2.9
6	99	200	95	40	141	13.0	1.1	138.0	9.8	3.6	3.0	4.8	32.0	25.0	4.9
7	104	169	137	51	91	10.0	0.6	141.0	9.6	3.7	2.8	4.2	22.0	25.0	4.8
8	129	190	85	60	113	9.0	0.9	138.0	9.5	4.0	2.5	5.0	35.0	50.0	4.5
9	105	225	90	67	140	16.0	1.1	139.0	8.9	3.5	5.3	4.2	30.0	33.0	3.7
10	95	166	115	40	103	9.0	0.8	141.0	9.8	3.9	4.4	3.6	33.0	29.0	3.9
11	110	235	290	40	137	18.0	0.8	136.0	8.9	3.7	2.9	4.6	25.0	33.0	3.2
12	99	230	120	88	118	12.0	0.6	140.0	9.8	3.5	4.0	4.0	40.0	35.0	3.5
13	100	190	105	50	119	11.0	1.0	142.0	10.0	3.5	3.2	4.5	20.0	15.0	4.3
14	112	180	170	35	111	19.0	1.2	143.0	9.1	3.3	2.4	4.3	25.0	30.0	3.7
15	96	204	246	47	108	14.0	1.0	142.0	9.4	3.6	3.4	4.2	35.0	43.0	3.8
16	115	197	90	55	124	18.0	0.9	139.0	9.7	4.0	2.9	4.1	55.0	40.0	4.5
17	99	225	120	55	146	26.0	1.4	143.0	10.2	3.1	3.5	4.5	40.0	35.0	3.0
18	98	197	82	62	118	12.0	0.7	144.0	9.7	4.7	3.4	4.7	25.0	20.0	4.0
19	102	201	125	50	126	15.0	1.4	140.0	9.9	3.8	3.1	4.5	25.0	37.0	4.5
20	106	240	100	67	153	19.0	1.1	138.0	9.5	4.3	3.2	4.7	18.0	29.0	4.0
21	118	220	114	46	151	19.0	1.2	145.0	9.1	4.6	3.3	4.7	18.0	20.0	3.7
22	97	227	87	57	153	15.0	0.9	140.0	9.6	4.0	3.6	4.5	21.0	19.0	6.3
23	112	250	220	45	161	16.0	1.0	145.0	9.6	3.7	4.0	5.0	18.0	25.0	5.0
24	91	210	120	42	144	10.0	0.8	145.0	9.9	3.9	2.5	4.1	20.0	21.0	5.9
25	96	177	85	58	102	15.0	1.0	140.0	10.3	4.2	4.4	4.3	19.0	13.0	6.4

BIOGRAPHY

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